



# Acta Medica Scandinavica

Supplementum 621

Abstracts of papers  
presented at  
The XXXVI Scandinavian Congress  
of Internal Medicine

June 1 – 3 1978  
Oslo Norway

*Edited by*  
*P Tølsberg and E Gjone*

# Acta Medica Scandinavica

originally published as *Nordiskt Medicinskt Arkiv* was founded in 1869 by Professor Axel Key MD. In 1901 (from volume 34) this journal was divided into a medical and a surgical section. Since 1919 (from volume 52) the medical section has been published under the name of *Acta Medica Scandinavica*.

## *Acta Medica Scandinavica*

publishes papers on general medicine mainly from Denmark, Finland, Iceland, Norway, Sweden and the Netherlands. Short preliminary reports (not exceeding two pages) will be published at short notice. The papers are published in English, French or German. *Acta Medica Scandinavica* is published on a non-profit basis.

## *Subscriptions*

to *Acta Medica Scandinavica* (two volumes of six numbers each annually) include free supplements to the current volumes.

## *Subscription Rates*

Per annum = two volumes

In Denmark, Finland, Iceland, Norway, Sweden and the Netherlands Sw. cr. 300 incl. postage. Swedish subscribers add VAT.  
Other countries Sw. cr. 345 incl. postage.

## *Chief Editor*

Professor Jan G. Waldenström MD  
*Acta Medica Scandinavica*  
Kungsgatan 54  
S-111 35 Stockholm, Sweden

## *Editorial Office*

*Acta Medica Scandinavica*  
Kungsgatan 54  
S-111 35 Stockholm, Sweden  
(All correspondence concerning manuscripts and editorial matters)  
Telephone 08/21 77 63

## *Subscription, Distribution and Advertising*

The Almqvist & Wiksell Periodical Company  
Gamla Brogatan 26, Box 62  
S-101 20 Stockholm 1, Sweden

## *Printers*

Almqvist & Wiksell Tryckeri AB  
S-751 81 Uppsala, Sweden

# Acta Medica Scandinavica

Supplementum 621

Abstracts of papers  
presented at  
The XXXVI Scandinavian Congress  
of Internal Medicine

June 1 – 3 1978  
Oslo Norway

*Edited by*  
*P Tølsberg and E Gjone*



# Acta Medica Scandinavica

originally published as *Nordiskt Medicinskt Arkiv* was founded in 1869 by Professor Axel Key MD. In 1901 (from volume 34) this journal was divided into a medical and a surgical section. Since 1919 (from volume 52) the medical section has been published under the name of *Acta Medica Scandinavica*.

## *Acta Medica Scandinavica*

publishes papers on general medicine mainly from Denmark, Finland, Iceland, Norway, Sweden and the Netherlands. Short preliminary reports (not exceeding two pages) will be published at short notice. The papers are published in English, French or German. *Acta Medica Scandinavica* is published on a non-profit basis.

## *Subscriptions*

to *Acta Medica Scandinavica* (two volumes of six numbers each annually) include free supplements to the current volumes.

## *Subscription Rates*

Per annum = two volumes

In Denmark, Finland, Iceland, Norway, Sweden and the Netherlands Sw. cr. 300 incl. postage. Swedish subscribers add VAT.

Other countries Sw. cr. 345 incl. postage.

## *Chief Editor*

Professor Jan G. Waldenström MD  
*Acta Medica Scandinavica*  
Kungsgatan 54  
S-111 35 Stockholm, Sweden

## *Editorial Office*

*Acta Medica Scandinavica*  
Kungsgatan 54  
S-111 35 Stockholm, Sweden  
(All correspondence concerning manuscripts and editorial matters)  
Telephone 08/21 77 63

## *Subscription Distribution and Advertising*

The Almqvist & Wiksell Periodical Company  
Gamla Brogatan 26, Box 62  
S-101 20 Stockholm 1, Sweden

## *Printers*

Almqvist & Wiksell Tryckeri AB  
S-751 81 Uppsala, Sweden

## CONTENTS

LIVER DISEASES	9 14
Bøhmer T (Oslo)	9
POSTOPERATIVE ICTERUS IN THE CARDIAC PATIENT	
Ritland S Fausa O and Elgjo K (Oslo)	10
LIVER DISEASE AS THE FIRST MANIFESTATION OF INFLAMMATORY BOWEL DISEASE	
Digranes O (Bergen)	11
LIVER BIOPSIES IN CHRONIC ALCOHOLISM ITS CONTRIBUTION TO CLINICAL AND LABORATORY DIAGNOSIS	
Ritland S Osen K and Rostad B (Oslo)	12
HEPATIC HYDROTHORAX	
Bell H and Nordhagen R (Oslo)	13
ASSOCIATION BETWEEN HLA B40 AND ALCOHOLIC LIVER DISEASE WITH CIRRHOSIS	
BLOOD DISEASES	15 - 19
Rofven O K Odegård O R and	14
Abildgaard U (Oslo)	
HAEMOSTATIC PROFILE IN A CLINICAL MATERIAL	
Ly B Arnesen H Eie H and Hol R (Oslo)	15
A PROSPECTIVE STUDY OF STREPTOKINASE AND HEPARIN IN THE TREATMENT OF MAJOR PULMONARY EMBOLISM	



# CONTENTS

LIVER DISEASES	9	14
Bohmer T (Oslo)		9
POSTOPERATIVE ICTERUS IN THE CARDIAC PATIENT		
Ritland S Fausa O and Elgjo K (Oslo)		10
LIVER DISEASE AS THE FIRST MANIFESTATION OF INFLAMMATORY BOWEL DISEASE		
Digranes O (Bergen)		11
LIVER BIOPSIES IN CHRONIC ALCOHOLISM ITS CONTRIBUTION TO CLINICAL AND LABORATORY DIAGNOSIS		
Ritland S Osen K and Rostad B (Oslo)		1
HEPATIC HYDROTHORAX		
Bell H and Nordhagen R (Oslo)		13
ASSOCIATION BETWEEN HLA B40 AND ALCOHOLIC LIVER DISEASE WITH CIRRHOSIS		
BLOOD DISEASES	15	19
Refven O K Odegård O R and Abildgaard U (Oslo)		14
HAEMOSTATIC PROFILE IN A CLINICAL MATERIAL		
Iy B Arnesen H Eie H and Hol R (Oslo)		15
A PROSPECTIVE STUDY OF STREPTOKINASE AND HEPARIN IN THE TREATMENT OF MAJOR PULMONARY EMBOLISM		



# CONTENTS

LIVER DISEASES	9	14
Bøhmer T (Oslo)		9
POSTOPERATIVE ICTERUS IN THE CARDIAC PATIENT		
Ritland S Fausa O and Elgjo K (Oslo)		10
LIVER DISEASE AS THE FIRST MANIFESTATION OF INFLAMMATORY BOWEL DISEASE		
Digranes O (Bergen)		11
LIVER BIOPSIES IN CHRONIC ALCOHOLISM ITS CONTRIBUTION TO CLINICAL AND LABORATORY DIAGNOSIS		
Ritland S Osen K and Rostad B (Oslo)		12
HEPATIC HYDROTHORAX		
Bell H and Nordhagen R (Oslo)		13
ASSOCIATION BETWEEN HLA B40 AND ALCOHOLIC LIVER DISEASE WITH CIRRHOSIS		
BLOOD DISEASES	15	- 19
Refvem O K Odgaard O R and Abildgaard U (Oslo)		14
HAEMOSTATIC PROFILE IN A CLINICAL MATERIAL		
Ly B Arnesen H Eie H and Hol R (Oslo)		15
A PROSPECTIVE STUDY OF STREPTOKINASE AND HEPARIN IN THE TREATMENT OF MAJOR PULMONARY EMBOLISM		



# CONTENTS

LIVER DISEASES	9	14
Böhmer T (Oslo)		9
POSTOPERATIVE ICTERUS IN THE CARDIAC PATIENT		
Ritland S Fausa O and Elgjo K (Oslo)		10
LIVER DISEASE AS THE FIRST MANIFESTATION OF INFLAMMATORY BOWEL DISEASE		
Digraanes Ø (Bergen)		11
LIVER BIOPSIES IN CHRONIC ALCOHOLISM ITS CONTRIBUTION TO CLINICAL AND LABORATORY DIAGNOSIS		
Ritland S Osen K and Rostad B (Oslo)		12
HEPATIC HYDROTHORAX		
Bell H and Nordhagen R (Oslo)		13
ASSOCIATION BETWEEN HLA B40 AND ALCOHOLIC LIVER DISEASE WITH CIRRHOSIS		
BLOOD DISEASES	15	19
Refvem O K Odegård O R and Abildgaard U (Oslo)		14
HAEMOSTATIC PROFILE IN A CLINICAL MATERIAL		
Ly M Arnosen H Eie H and Hol R (Oslo)		15
A PROSPECTIVE STUDY OF STREPTOKINASE AND HEPARIN IN THE TREATMENT OF MAJOR PULMONARY EMBOLISM		



Holm H A Abildgaard, U and  
Bjerkelund Chr (Oslo)

HEPARIN TREATMENT OF DEEP VENOUS THROMBOSIS  
(DVT) CLINICAL VALUES OF HEPARIN ASSAYS

Wisløff F (Oslo)

HAEMOLYTIC ANAEMIA IN ALCOHOL ABUSE  
A REVIEW OF 14 CASES

Arnesen H Heilo A Jakobsen E  
Ly B and Skaga E (Oslo)

A PROSPECTIVE STUDY OF STREPTOKINASE AND  
HEPARIN IN THE TREATMENT OF DEEP VEIN  
THROMBOSIS

Ødegård O R and Abildgaard U (Oslo)  
CLINICAL SIGNIFICANCE OF ANTIFACTOR Xa  
ASSAY

#### CARDIOVASCULAR DISEASES

Hämäläinen H Kallio V and Vuori I  
(Turku)

THE PROGNOSTIC VALUE OF LOW LEVEL EXERCISE  
TEST AFTER ACUTE MYOCARDIAL INFARCTION

Kringlen E (Oslo)

STRESS PERSONALITY AND CORONARY HEART  
DISEASE - A TWIN STUDY

Luoma P V Kujala P A and Takkunen J T  
(Oulu)

INTRAVENOUS DISOPYRAMIDE IN THE CONVERSION  
OF SUPRAVENTRICULAR ARRHYTHMIAS INTO SINUS

Forfang K Rostad H and Sørland S (Oslo)	22
LONG TERM PROGNOSIS AFTER SURGICAL CORRECTION OF COARCTATION OF THE AORTA	
Madsen B B Rasmussen S and Svendsen T L (Glostrup)	23
PROGNOSTIC INDEX FOR EARLY DISCHARGE IN ACUTE MYOCARDIAL INFARCTION	
Miah K Britton M de Faire U Holmers C Ryding C and Wester P O (Stockholm)	24
CARDIAC ARRHYTHMIAS IN PATIENTS WITH ACUTE CEREBROVASCULAR DISEASE	
CARDIOVASCULAR DISEASES AND HYPERTENSION	25 28
Nesje O A and Lovorstad K O (Oslo)	25
EVALUATION OF LEFT VENTRICULAR FUNCTION BY ECHOCARDIOGRAPHY	
Isalch B and Oust Paulsen A (Oslo)	6
HYGROTON <sup>(R)</sup> IN ESSENTIAL HYPERTENSION EFFECT OF HYGROTON ON CARDIAC OUTPUT RENAL PLASMA FLOW [ RENIN AND ALDOSTERONE	
de Faire U Britton M Holmers C and Wester P O (Stockholm Umeå)	7
BLOOD PRESSURE DURING THE ACUTE PHASES OF CEREBROVASCULAR DISEASE	
Isalch B and Norman A (Oslo)	8
ANGIOTENSIN II BLOCKADE (SARALASIN) IN COMBINATION WITH RADIOGRAPHY IN THE DIAGNOSIS OF RENOVASCULAR HYPERTENSION	

Holm, H A , Abildgaard U and  
Bjerkelund, Chr (Oslo)

HEPARIN TREATMENT OF DEEP VENOUS THROMBOSIS  
(DVT) CLINICAL VALUES OF HEPARIN ASSAYS

Wisløff F (Oslo)

HAEMOLYTIC ANAEMIA IN ALCOHOL ABUSE  
A REVIEW OF 14 CASES

Arnesen H Hello A Jakobsen E  
Ly B and Skaga E (Oslo)

A PROSPECTIVE STUDY OF STREPTOKINASE AND  
HEPARIN IN THE TREATMENT OF DEEP VEIN  
THROMBOSIS

Ødegård O R and Abildgaard U (Oslo)  
CLINICAL SIGNIFICANCE OF ANTIFACTOR Xa  
ASSAY

#### CARDIOVASCULAR DISEASES

Hämäläinen H Hallio V and Vuori I  
(Turku)

THE PROGNOSTIC VALUE OF LOW LEVEL EXERCISE  
TEST AFTER ACUTE MYOCARDIAL INFARCTION

Kringlen E (Oslo)

STRESS PERSONALITY AND CORONARY HEART  
DISEASE - A TWIN STUDY

Luoma P V Lujala P A and Takkunen J T  
(Oulu)

INTRAVENOUS DISOPYRAMIDE IN THE CONVERSION  
OF SUPRAVENTRICULAR ARRHYTHMIAS INTO SINUS  
RHYTHM

Forfang K Rostad H and Sørland S (Oslo)	22
LONG TERM PROGNOSIS AFTER SURGICAL CORRECTION OF COARCTATION OF THE AORTA	
Madsen E H Rasmussen S and Svendsen T L (Glostrup)	23
PROGNOSTIC INDEX FOR EARLY DISCHARGE IN ACUTE MYOCARDIAL INFARCTION	
Mish K Britton M de Faire U Helmers C Ryding C and Wester P O (Stockholm)	24
CARDIAC ARRHYTHMIAS IN PATIENTS WITH ACUTE CEREBROVASCULAR DISEASE	
CARDIOVASCULAR DISEASES AND HYPERTENSION	25 28
Nesje O A and Levorstad K O (Oslo)	25
EVALUATION OF LEFT VENTRICULAR FUNCTION BY ECHOCARDIOGRAPHY	
Isleth D and Quist Paulsen A (Oslo)	26
HYGROTON <sup>(R)</sup> IN ESSENTIAL HYPERTENSION EFFECT OF HYGROTON ON CARDIAC OUTPUT REAL PLASMA FLOW RENIN AND ALDOSTERONE	
de Faire U Britton H Helmers C and Wester P O (Stockholm Umeå)	7
BLOOD PRESSURE DURING THE ACUTE PHASES OF CEREBROVASCULAR DISEASE	
Isleth D and Norman A (Oslo)	8
ANGIOTENSIN II BLOCKADE (SARALASIN) IN COMBINATION WITH RENOGRAPHY IN THE DIAGNOSIS OF RENOVASCULAR HYPERTENSION	

Holm H A Abildgaard U and  
Bjerkelund Chr (Oslo)

HEPARIN TREATMENT OF DEEP VENOUS THROMBOSIS  
(DVT) CLINICAL VALUES OF HEPARIN ASSAYS

Wisløff F (Oslo)

HAEMOLYTIC ANAEMIA IN ALCOHOL ABUSE  
A REVIEW OF 14 CASES

Arnesen H Hello A , Jakobsen E  
Ly, B and Skaga, E (Oslo)

A PROSPECTIVE STUDY OF STREPTOKINASE AND  
HEPARIN IN THE TREATMENT OF DEEP VEIN  
THROMBOSIS

Odegård O R and Abildgaard U (Oslo)  
CLINICAL SIGNIFICANCE OF ANTIFACTOR Xa  
ASSAY

#### CARDIOVASCULAR DISEASES

Hämäläinen H Kallio V and Vuori I  
(Turku)

THE PROGNOSTIC VALUE OF LOW LEVEL EXERCISE  
TEST AFTER ACUTE MYOCARDIAL INFARCTION

Kringlen E (Oslo)

STRESS PERSONALITY AND CORONARY HEART  
DISEASE - A TWIN STUDY

Luoma P V Kujala P A and Takkinen J T  
(Oulu)

INTRAVEINOUS DISOPYRAMIDE IN THE CONVERSION  
OF SUPRAVENTRICULAR ARRHYTHMIAS INTO SINUS  
RHYTHM

Hellum K B and Lehmann V (Bergen)	35
PENETRATION OF BENZYL PENICILLIN TO HUMAN TISSUE FLUID IN SUBCUTANEOUS WICKS AND SKIN BLISTERS	
Vissen Meyer R (Oslo)	36
ADJUVANT CYTOSTATIC CHEMOTHERAPY AFTER MASTECTOMY FOR BREAST CANCER TREATMENT FOR ONE WEEK OR FOR ONE YEAR?	
CARDIOVASCULAR DISEASES PULMONARY DISEASES	37 - 41
Murray V Britton M de Faire U	37
Helmers C and Wester P O (Stockholm Umeå)	
CORRECTNESS OF BEDSIDE DIAGNOSIS IN CEREBROVASCULAR DISEASE	
Asmussen I (København)	38
VESSEL DAMAGE CAUSED BY TOBACCO-SMOKING IN HUMANS	
Agner E Hannover Larsen J and Leth A (Glostrup Gentofte)	39
YERSINIA ENTERCOLITICA CARDITIS AS A DIFFERENTIAL DIAGNOSIS AND THE PROGNOSIS OF THIS DISEASE	
Gulsvik A (Oslo)	40
SPIROMETRY IN AN URBAN NORDIC POPULATION Aged 0-9 YEARS	

## METABOLISM

Henriksen T Evensen S A and  
Carlander B (Oslo)

INDUCTION AND INHIBITION OF INJURY TO  
HUMAN ENDOTHELIAL CELLS IN CULTURE  
MEDIATED BY PLASMA LIPOPROTEINS

Noppa H and Bengtsson C (Göteborg)  
OBESITY IN RELATION TO SMOKING  
A CROSS-SECTIONAL AND LONGITUDINAL  
STUDY OF WOMEN IN GÖTEBORG SWEDEN

Brinch L Teisberg P and Akesson I  
(Oslo)  
METABOLIC C3 STUDIES IN MAN

Frøyskov Larsen I Hansen E and  
Berg A (Oslo)  
DEGENERATIVE LIVER DISEASE AND ENDOCRINE  
DYSFUNCTION IN PATIENTS WITH PROGRESSIVE  
CONGENITAL DYSTROPHY

## PHARMACOTHERAPY AND TOXICOLOGY

Amlie J P (Oslo)  
THE INOTROPIC AND ELECTROPHYSIOLOGIC  
EFFECTS OF DIGITOXIN COMPARED TO DIGOXIN  
IN THE DOG HEART IN SITU

Skjott J Teisberg P Bredesen J E  
and Lunde P K M (Oslo)  
A PROSPECTIVE STUDY OF INTOXICATIONS WITH  
TRICYCLIC ANTIDEPRESSANT AGENTS (TCA)

Hellum K B and Lehmann V (Bergen)	35
PENETRATION OF BENZYL PENICILLIN TO HUMAN TISSUE FLUID IN SUBCUTANEOUS WICKS AND SKIN BLISTERS	
Nissen Meyer R (Oslo)	36
ADJUVANT CYTOSTATIC CHEMOTHERAPY AFTER MASTECTOMY FOR BREAST CANCER TREATMENT FOR ONE WEEK OR FOR ONE YEAR?	
CARDIOVASCULAR DISEASES    PULMONARY DISEASES	37    41
Murray V    Britton M    de Faire U	37
Holmers C    and Wester P O (Stockholm    Umeå)	
CORRECTNESS OF BEDSIDE DIAGNOSIS IN CEREBROVASCULAR DISEASE	
Asmussen I (København)	38
VESSEL DAMAGE CAUSED BY TOBACCO-SMOKING IN INDIANS	
Agner E    Hannover Larsen J    and Leth A (Glostrup    Gentofte)	39
VERSILIA ENTERCOLITICA CARDITIS AS A DIFFERENTIAL DIAGNOSIS    AND THE PROGNOSIS OF THIS DISEASE	
Gulsvik A (Oslo)	40
SPIROMETRY IN AN URBAN NORDIC POPULATION AGED 0-0 YEARS	



Agner E Hagerup L From Hansen R  
Lønberg F and Schroll M (Glostrup)  
A TEN-YEAR PROSPECTIVE STUDY OF RESPIRATORY  
SYMPTOMS AND PULMONARY FUNCTION IN 50 AND  
60 YEAR OLDS

#### GASTROENTEROLOGICAL DISEASES

Hess Thaysen, E (Aalborg)  
CHOLEGENIC DIARRHOEA IN THE IRRITABLE  
COLON SYNDROME

Valnes K Myren J and Qvigstad T  
(Oslo)  
TRIMIPRAMINE IN THE TREATMENT OF GASTRIC  
ULCER

Higa H J Andersen K J Schjønby H  
and Skagen D W (Bergen)  
ENZYME ACTIVITIES IN JEJUNAL BIOPSIES IN  
PATIENTS WITH ATYPICAL COELIAC DISEASE

Bjørneklett A Fausa O Løvik A  
Ritland S and Gjone E (Oslo)  
FIBRE TABLETS AS EFFECTIVE ALTERNATIVE TO  
WHEAT BRAN IN CHRONIC CONSTIPATION

Störtebecker T P (Stockholm)  
COMMON INTESTINAL BACTERIA IN ETIOLOGY OF  
COLON CANCER

Bell, H Orjasæter H and Lange H F  
(Oslo)  
CARCINOEMBRYONIC ANTIGEN (CEA) IN LIVER  
DISEASE AND ITS RELATION TO DIFFERENT  
LIVER FUNCTION TESTS

# POSTOPERATIVE ICTERUS IN THE CARDIAC PATIENT

Thomas Bohner,

Dept Med B, Rikshospitalet, Oslo, Norway

Two to five per cent of patients operated with heart-lung machine develop postoperatively a cholestatic syndrome with increase in bilirubin (70 % conjugated) and only moderate increase in ASAT and ALAT. The increased bilirubin level returns usually to normal within 2-5 weeks. An increase in bilirubin level after the 10 postoperative day is a bad prognostic sign. There are few biochemical signs of the cholestasis which was confirmed by liver biopsy.

23 patients who developed postoperative icterus had a mean heart size of  $750 \text{ ml/m}^2$  and a cardiac index of only  $2.25 \text{ l/min/m}^2$ . Such patients have a severely reduced cardiac function preoperatively and are susceptible to circulatory disturbances pre/postoperatively.

Postoperative icterus occurs more frequently in patients with mitral valve prosthesis than with aortic valve or SD/ASD or coronary bypass who are all operated with heart lung machine. Bilirubin elimination measured with steady state technique showed that mitral valve patients had a reduced capacity to eliminate bilirubin preoperatively ( $T_1/2$  75-150 min) compared to control group ( $T_1/2$  30-75 min).

In the cholestatic syndrome which occurs as a result of circulatory disturbances there is also a reduced ability of the reticuloendothelial system to remove endotoxins and the incomplete transport of bilirubin to the gut facilitates resorption of endotoxins from the intestine. It is possible therefore that endotoxins from infections in the urinary system or airways (E coli, Proteus, Klebsiella) or from the normal gut will further reduce the liver function.

Liver function is most likely not caused by Halothane anesthesia, by virus infection (Australia antigen) or by blood transfusions. Numerous blood transfusions however is an expression of the unstable circulatory situation. The cholestatic syndrome is multifactorial due to pre/postoperative circulatory disturbances and possibly due also to endotoxins.

Agner E Hagerup L , From Hansen R  
Lønberg F and Schroll M (Glostrup)  
A TEN-YEAR PROSPECTIVE STUDY OF RESPIRATORY  
SYMPTOMS AND PULMONARY FUNCTION IN 50 AND  
60 YEAR OLDS

## GASTROENTEROLOGICAL DISEASES

Hess Thaysen E (Aalborg)  
CHOLEGENIC DIARRHOEA IN THE IRRITABLE  
COLON SYNDROME

Valnes A Myren J and Qvigstad T  
(Oslo)  
TRIMIPRAMINE IN THE TREATMENT OF GASTRIC  
ULCER

Haga H J Andersen A J Schjønby H  
and Skagen D W (Bergen)  
ENZYME ACTIVITIES IN JEJUNAL BIOPSIES IN  
PATIENTS WITH ATYPICAL COELIAC DISEASE

Bjørnklepp A Fausa O Løvik A  
Ritland S and Gjone E (Oslo)  
FIBRE TABLETS AS EFFECTIVE ALTERNATIVE TO  
WHEAT BRAN IN CHRONIC CONSTIPATION

Störtebecker T P (Stockholm)  
COMMON INTESTINAL BACTERIA IN ETIOLOGY OF  
COLON CANCER

Bell H Ørjasæter H and Lange H F  
(Oslo)  
CARCINOEMBRYONIC ANTIGEN (CEA) IN LIVER  
DISEASE AND ITS RELATION TO DIFFERENT  
LIVER FUNCTION TESTS

# POSTOPERATIVE ICTERUS IN THE CARDIAC PATIENT

Thomas Böhmer,

Dept Med B, Rikshospitalet, Oslo, Norway

Two to five per cent of patients operated with heart lung machine develop postoperatively a cholestatic syndrome with increase in bilirubin (70 % conjugated) and only moderate increase in ASAT and ALAT. The increased bilirubin level returns usually to normal within 2-5 weeks. An increase in bilirubin level after the 10 postoperative day is a bad prognostic sign. There are few biochemical signs of the cholestasis which was confirmed by liver biopsy.

23 patients who developed postoperative icterus had a mean heart size of 750 ml/m<sup>2</sup> and a cardiac index of only 2.25 l/min/m<sup>2</sup>. Such patients have a severely reduced cardiac function preoperatively and are susceptible to circulatory disturbances pre/postoperatively.

Postoperative icterus occurs more frequently in patients with mitral valve prosthesis than with aortic valve or SD/VSD or coronary bypass who are all operated with heart lung machine. Bilirubin elimination measured with steady state technique showed that mitral valve patients had a reduced capacity to eliminate bilirubin preoperatively ( $T_{1/2}$  75-150 min) compared to control group ( $T_{1/2}$  30-75 min).

In the cholestatic syndrome which occurs as a result of circulatory disturbances there is also a reduced ability of the reticuloendothelial system to remove endotoxins and the incomplete transport of bilirubin to the gut facilitates resorption of endotoxins from the intestine. It is possible therefore that endotoxins from infections in the urinary system or airways (E. coli, Proteus, Klebsiella) or from the normal gut will further reduce the liver function.

Liver function is most likely not caused by Halothane anesthesia, by virus infection (Australia antigen) or by blood transfusions. Numerous blood transfusions however is an expression of the unstable circulatory situation. The cholestatic syndrome is multifactorial due to pre/per/postoperative circulatory disturbances and possibly due also to endotoxins.

# LIVER DISEASE AS THE FIRST MANIFESTATION OF INFLAMMATORY BOWEL DISEASE

S. Ritland, O. Fausa and K. Elgjo

Medical Department A and Department of Pathology,  
National Hospital of Norway, Rikshospitalet, Oslo 1, Norway

Abnormal liver function tests and morphological changes in the liver are well known complications of inflammatory bowel disease occurring in about 15 % of the patients. Usually the bowel disease starts several years prior to the demonstration of liver involvement. Occasionally the reverse is seen. We have recently observed three patients with cholestatic liver disorder found to be associated with asymptomatic ulcerative colitis. At the age of ten years biliary cirrhosis was diagnosed in the first patient. Her serum transaminases were slightly and the alkaline phosphatases markedly elevated. Five years later pericholangitis was demonstrated in liver biopsy. Further investigations revealed a symptomless chronic ulcerative colitis. Chronic active hepatitis was diagnosed in a fragmented liver biopsy specimen from the second patient, a 30 years old woman, and this led to longlasting treatment with corticosteroids. Ten years later liver biopsy showed histological changes as seen in patients with ulcerative colitis. Further examinations confirmed this diagnosis. By a routine checkup a 34 years old male was found to have elevated alkaline phosphatases. Liver biopsy demonstrated biliary cirrhosis and subsequent investigations revealed an asymptomatic ulcerative colitis.

In patients with cholestatic liver disorders and histological evidence of pericholangitis appropriate investigations for inflammatory bowel disease should be performed.

LIVER BIOPSIES IN CHRONIC ALCOHOLISM ITS CONTRIBUTION  
TO CLINICAL AND LABORATORY DIAGNOSIS  
Oyvind Digraes,  
Hjeltestad Klinikken, Bergen, Norway

A survey is given of the result of 220 liver biopsies in 212 men and 8 women with chronic alcoholism and clinical signs of liver disease

Cirrhosis was found in 29 patients (13.2 %) alcoholic hepatitis in 36 patients (16.4 %) fatty infiltration in 104 patients (47.3 %) 44 patients (20 %) had non specific signs of degeneration and repair in 5 patients the liver was found normal and in 2 patients the biopsy specimen was too small for an exact diagnosis

The relationship between the liver function tests and the diagnosis is discussed Gamma GT is found to be a much more sensitive test of alcoholic liver disease than ASAT and ALAT

Adequate nutrition was found in 60 % of the patients inadequate in 40 % but good or poor diet does not seem to be of major importance with regard to whether alcoholics will develop serious liver disease or not The amount of alcohol and the duration of the abuse is most important not the kind of alcohol

Even if there are few women in this study the results indicate a worse prognosis in female alcoholics 3 of 8 had cirrhosis 2 alcoholic hepatitis and 3 fatty infiltration

Except for a 56 year old woman who got an intra abdominal bleeding and had to go through a laparotomy there were no serious complications

# LIVER DISEASE AS THE FIRST MANIFESTATION ON INFLAMMATORY BOWEL DISEASE

S. Ritland, O. Fausa and A. Elgjo

Medical Department A and Department of Pathology,  
National Hospital of Norway, Rikshospitalet, Oslo 1, Norway

Abnormal liver function tests and morphological changes in the liver are well known complications of inflammatory bowel disease occurring in about 15 % of the patients. Usually the bowel disease starts several years prior to the demonstration of liver involvement. Occasionally the reverse is seen. We have recently observed three patients with cholestatic liver disorder found to be associated with asymptomatic ulcerative colitis. At the age of ten years biliary cirrhosis was diagnosed in the first patient. Her serum transaminases were slightly and the alkaline phosphatases markedly elevated. Five years later pericholangitis was demonstrated in liver biopsy. Further investigations revealed a symptomless chronic ulcerative colitis. Chronic active hepatitis was diagnosed in a fragmented liver biopsy specimen from the second patient, a 30 years old woman, and this led to longlasting treatment with corticosteroids. Ten years later liver biopsy showed histological changes as seen in patients with ulcerative colitis. Further examinations confirmed this diagnosis. By a routine checkup a 34 years old male was found to have elevated alkaline phosphatases. Liver biopsy demonstrated biliary cirrhosis and subsequent investigations revealed an asymptomatic ulcerative colitis.

In patients with cholestatic liver disorders and histological evidence of pericholangitis appropriate investigations for inflammatory bowel disease should be performed.

# LIVER BIOPSIES IN CHRONIC ALCOHOLISM ITS CONTRIBUTION TO CLINICAL AND LABORATORY DIAGNOSIS

Oyvind Digraes,

Hjellestad klinikken, Bergen, Norway

A survey is given of the results of 270 liver biopsies in 212 men and 8 women with chronic alcoholism and clinical signs of liver disease

Cirrhosis was found in 29 patients (13.2 %) alcoholic hepatitis in 36 patients (16.4 %) fatty infiltration in 104 patients (47.3 %) 44 patients (20 %) had non specific signs of degeneration and repair in 5 patients the liver was found normal and in 2 patients the biopsy specimen was too small for an exact diagnosis

The relationship between the liver function tests and the diagnosis is discussed Gamma GT is found to be a much more sensitive test of alcoholic liver disease than ASAT and ALAT

Adequate nutrition was found in 60 % of the patients inadequate in 40 % but good or poor diet does not seem to be of major importance with regard to whether alcoholics will develop serious liver disease or not The amount of alcohol and the duration of the abuse is most important not the kind of alcohol

Even if there are few women in this study the results indicate a worse prognosis in female alcoholics 3 of 8 had cirrhosis 7 alcoholic hepatitis and 3 fatty infiltration

Except for a 56 year old woman who got an intra abdominal bleeding and had to go through a laparotomy there were no serious complications



# LIVER DISEASE AS THE FIRST MANIFESTATION ON INFLAMMATORY BOWEL DISEASE<sup>1</sup>

S. Ritland, O. Fausa and A. Elgjo

Medical Department A and Department of Pathology,  
National Hospital of Norway, Rikshospitalet, Oslo 1, Norway

Abnormal liver function tests and morphological changes in the liver are well known complications of inflammatory bowel disease occurring in about 15 % of the patients. Usually the bowel disease starts several years prior to the demonstration of liver involvement. Occasionally the reverse is seen. We have recently observed three patients with cholestatic liver disorder found to be associated with asymptomatic ulcerative colitis. At the age of ten years biliary cirrhosis was diagnosed in the first patient. Her serum transaminases were slightly and the alkaline phosphatases markedly elevated. Five years later pericholangitis was demonstrated in liver biopsy. Further investigations revealed a symptomless chronic ulcerative colitis. Chronic active hepatitis was diagnosed in a fragmented liver biopsy specimen from the second patient, a 30 years old woman, and this led to longlasting treatment with corticosteroids. Ten years later liver biopsy showed histological changes as seen in patients with ulcerative colitis. Further examinations confirmed this diagnosis. By a routine checkup a 34 years old male was found to have elevated alkaline phosphatases. Liver biopsy demonstrated biliary cirrhosis, and subsequent investigations revealed an asymptomatic ulcerative colitis.

In patients with cholestatic liver disorders and histological evidence of pericholangitis appropriate investigations for inflammatory bowel disease should be performed.

# LIVER BIOPSIES IN CHRONIC ALCOHOLISM ITS CONTRIBUTION TO CLINICAL AND LABORATORY DIAGNOSIS

Arvid Digranes,

Jellestad klinikken, Bergen, Norway

A survey is given of the results of 220 liver biopsies in 212 men and 8 women with chronic alcoholism and clinical signs of liver disease

Cirrhosis was found in 29 patients (13.2 %) alcoholic hepatitis in 36 patients (16.4 %) fatty infiltration in 104 patients (47.3 %) 44 patients (20 %) had non specific signs of degeneration and repair in 5 patients the liver was found normal and in 2 patients the biopsy specimen was too small for an exact diagnosis

The relationship between the liver function tests and the diagnosis is discussed Gamma-GT is found to be a much more sensitive test of alcoholic liver disease than ASAT and ALAT

Adequate nutrition was found in 60 % of the patients inadequate in 40 % but good or poor diet does not seem to be of major importance with regard to whether alcoholics will develop serious liver disease or not The amount of alcohol and the duration of the abuse is most important not the kind of alcohol

Even if there are few women in this study the results indicate a worse prognosis in female alcoholics 3 of 8 had cirrhosis 2 alcoholic hepatitis and 3 fatty infiltration

Except for a 56 year old woman who got an intra abdominal bleeding and had to go through a laparotomy there were no serious complications

## HEPATIC HYDROTHORAX

S. Ritland, K. Osen & B. Rostad,

Medical Department A, Department of Pathology and  
Department of Radiology, National Hospital of Norway,  
Rikshospitalet, Oslo 1

Hydrothorax has long been recognized as a complication of cirrhosis of the liver. Its origin is not fully established. Most agree that ascites forms the hydrothorax across the diaphragm either through a diaphragmatic defect or through the diaphragmatic lymphatics. We have had the opportunity to study more carefully one patient with hepatic hydrothorax. A thirty-eight year old female had been treated for 13 years with corticosteroids for chronic active hepatitis when ascites and right-sided hydrothorax developed. For about two years treatment with salt restriction and diuretics was successful. During the last months however the liver functions deteriorated. Repeated thoracocentesis had to be performed due to rapidly reproducing hydrothorax.

Autopsy demonstrated pleural effusion on the right side (1700 ml) but not on the left side and ascites (400 ml). No holes or defects in the right hemidiaphragm was found. A 2 cm bleb was seen bulging into the pleural cavity. Microscopically, the inside of the bleb was covered by mesothelium underlined by dilated lymphatics. Mediastinal lymph nodes also showed lymphostasis.

In this patient the hydrothorax may be due to increased transport of fluid through the diaphragmatic lymphatics from the peritoneal to the pleural cavity.

# ASSOCIATION BETWEEN HLA B40 AND ALCOHOLIC LIVER DISEASE WITH CIRRHOSIS

H. Bell and R. Nordhagen,

Kroghstøtten Department of Oslo City Hospital, Oslo and Immunological Department, National Institute of Public Health, Oslo, Norway

HLA antigens were determined in 41 patients with alcoholic liver disease. The frequency of HLA B40 in 25 patients with alcoholic liver disease with cirrhosis confirmed by liver biopsy was significantly increased (52 %) in comparison with the frequency found in 153 healthy blood donors (18 %). The HLA-B40 frequency was not increased in 16 patients with alcoholic liver disease without cirrhosis (19 %) nor in a group of 16 patients with miscellaneous liver diseases (19 %). We could not confirm the previously reported association between advanced alcoholic liver damage and HLA B8 which has been taken as a support for the relation to autoimmune mechanisms. The association with HLA-B40 may support the idea that individual susceptibility to the development of alcoholic liver cirrhosis is genetically determined.

So far we have investigated 100 patients with alcoholic liver disease and the results obtained are confirmed.

## HEPATIC HYDROTHORAX

S. Ritland, K. Osen & B. Rostad,  
Medical Department A, Department of Pathology and  
Department of Radiology, National Hospital of Norway,  
Rikshospitalet, Oslo 1

Hydrothorax has long been recognized as a complication of cirrhosis of the liver. Its origin is not fully established. Most agree that ascites forms the hydrothorax across the diaphragm either through a diaphragmatic defect or through the diaphragmatic lymphatics. We have had the opportunity to study more carefully one patient with hepatic hydrothorax. A thirty-eight year old female had been treated for 13 years with corticosteroids for chronic active hepatitis, when ascites and right-sided hydrothorax developed. For about two years treatment with salt restriction and diuretics was successful. During the last months however the liver functions deteriorated. Repeated thoracocentesis had to be performed due to rapidly reproducing hydrothorax.

Autopsy demonstrated pleural effusion on the right side (1700 ml) but not on the left side and ascites (400 ml). No holes or defects in the right hemidiaphragm was found. A 2 cm bleb was seen bulging into the pleural cavity. Microscopically the inside of the bleb was covered by mesothelium underlined by dilated lymphatics. Mediastinal lymph nodes also showed lymphostasis.

In this patient the hydrothorax may be due to increased transport of fluid through the diaphragmatic lymphatics from the peritoneal to the pleural cavity.

# A PROSPECTIVE STUDY OF STREPTOKINASE AND HEPARIN IN THE TREATMENT OF MAJOR PULMONARY EMBOLISM

E. Ly, H. Arnesen, H. Eie and R. Hol,

Medical Department IX and Department of Radiology,  
Ullevål Hospital, University Clinic, Oslo, Norway

Treatment with streptokinase or heparin was allocated randomly to 25 patients with major pulmonary embolism verified by angiography. Only patients with a history of less than five days and with major embolism affecting at least one lobar artery were included.

Standard doses of streptokinase or heparin were given for 72 hours and pulmonary angiography was then repeated.

The severity of the pulmonary artery occlusion was interpreted by a score system devised by Miller et al (Br J Med 2: 681, 1971). The mean angiographic score fell 52.3% in 14 streptokinase treated patients compared with only 20.5% in 11 patients treated with heparin. Using the Student's t test, this difference is statistically highly significant ( $p < 0.01$ ). In the streptokinase group 8 of 10 patients with massive embolism (angiographic score above 20) showed substantial thrombolysis compared with only 2 of 6 patients in the heparin group.

In the heparin group 1 patient died from massive embolism 15 hours after the start of treatment and in another patient who died 4 weeks later, persistent massive embolism contributed to the fatal outcome.

In the streptokinase group 1 patient died 3 weeks after the start of treatment from gangrene of both legs following thrombotic occlusion of the inferior vena cava.

Bleeding was more common after treatment with streptokinase than with heparin but was not a serious problem in any patient. The increased bleeding tendency in the streptokinase group was related to puncture or cut-down sites whereas spontaneous bleeding was equally common in the two groups.

It is concluded that patients with life threatening pulmonary embolism should be offered the benefits of streptokinase.

HAEMOSTATIC PROFILE IN A CLINICAL MATERIAL  
O K Refvem, O R Ødegård and U Abildgaard,  
Medical Department A, Aker Hospital, Oslo 5, Norway

During 1977 1310 blood samples were analyzed as follows Thrombocyte count fibrinogen concentration Fibrin gelation test Normotest Thrombotest Activated Partial Thromboplastin Time (APTT) Antithrombin III (At), heparin, Fibrin Degradation Product (FDP) Thrombin clotting time Based on the results a coagulation profile was defined for each sample

Suspected thrombo-embolism was the most frequent reason for consultation followed by bleeding control of heparin therapy suspected disseminated intravascular coagulation (DIC) and liver disease

In verified thrombosis increased FDP was found in all but one case Subnormal At was found in some of these patients Thrombocytopenia increased fibrinolysis often with hypercoagulation were the most frequent abnormalities in bleeding patients Only two haemophiliacs were encountered In many patients generalized bleeding tendency was ruled out

Heparin levels below a defined therapeutic range (0.2-0.7 U/ml) were found in more than half the samples from treated patients suggesting underdosage

Signs of DIC were also encountered in samples referred because of bleeding or thrombosis The At concentration tended to decrease with increasing degree of consumption coagulopathy (thrombocytopenia hypofibrinogenaemia high FDP) Occasionally subnormal At levels were found in the absence of frank DIC A study of the case records revealed that most of these patients had undergone hypoperfusion syndromes possibly complicated by DIC

The major value of this laboratory service is in the examination of the bleeding patient and the patient with DIC

HAEMOLYTIC ANAEMIA IN ALCOHOL ABUSE A REVIEW OF 14 CASES  
F Wisløff,  
Ullevål Hospital, Krohgstøtten Dept., Oslo, Norway

Clinical and haematological data on 14 patients (eight women and six men) with alcohol-induced haemolytic anaemia and mild to moderate liver injury are presented. Nine of the patients were obvious drinkers while five were socially well adjusted individuals in whom alcohol dependence was not suspected on admission to hospital. Four patients presented with typical Zieve's syndrome. Two further patients had a moderate transient stomatocytosis as assessed by microscopy of dried blood smears and by scanning electron microscopy. The majority of the patients however did not fit into any of the syndromes proposed in the literature. Indeed the validity of both Zieve's syndrome and the "transient stomatocytosis with haemolysis" syndrome is questioned.



# HEPARIN TREATMENT OF DEEP VEIN THROMBOSIS (DVT) CLINICAL VALUES OF HEPARIN ASSAYS

H A Holm, U Abildgaard and Chr Bjerkelund  
Med Dep A, Aker Hospital, Oslo 5, Norway

In a multi center trial patients with phlebo graphically verified DVT are given continuous heparin infusion for at least 5 days. Blood samples are drawn daily for determination of heparin by 3 different methods:  
1) APTT - a global test reflecting heparin effect on the intrinsic system (Cephotest<sup>R</sup>)  
2) Thrombin time and  
3) An amidolytic assay for determination of heparin concentration (1) (Coatest<sup>R</sup>). The study is still in progress and this report is preliminary (1 Teien Thromb Res 8 1976)

Of 120 patients admitted to the trial 4 patients have suffered serious bleedings requiring blood transfusion. In one patient an intrathoracic bleeding - probably caused by a thoracocentesis - contributed to a fatal outcome 7 days after onset of heparin therapy. Heparin was in the lower part of therapeutic range as determined by all three assays.

The three non-fatal bleedings had average heparin conc (amidolytic assay) above therapeutic range (0,2 - 0,7 U/ml). APTT-values were above therapeutic range (>120 sec) two days or more in the non-fatal bleedings.

1/5 of the total material had average heparin conc above therapeutic range and 1/4 had two or more APTT-values above therapeutic range.

Thrombin time in patients with bleedings did not differ significantly from the rest of the material.

Thrombocytopenia has been reported in a great proportion of patients receiving heparin prepared from bovine lung (2). In our study all patients are treated with heparin prepared from porcine mucosa (Heparin Nyco<sup>R</sup>). Thrombocytopenia has been recorded in only one patient. This patient died from pulmonary embolism without signs of bleeding. Other hemostatic parameters indicated consumption coagulopathy (DIC) (2 Bell Ann Intern Med 1976 85, 155-160).

We conclude that thrombocytopenia does not seem to represent a major problem with the type of heparin used in this study.

Our preliminary results indicate that amidolytic assay and APTT may be of value in monitoring heparin therapy by decreasing the risk of bleeding complications. Thrombin time assay does not seem to have this property.

HAEMOLYTIC ANAEMIA IN ALCOHOL ABUSE A REVIEW OF 14 CASES  
F. Wisløff,  
Ullevål Hospital, Krohgstøtten Dept., Oslo, Norway

Clinical and haematological data on 14 patients (eight women and six men) with alcohol induced haemolytic anaemia and mild to moderate liver injury are presented. Nine of the patients were obvious drinkers while five were socially well adjusted individuals in whom alcohol dependence was not suspected on admission to hospital. Four patients presented with typical Zieve's syndrome. Two further patients had a moderate transient stomatocytosis as assessed by microscopy of dried blood smears and by scanning electron microscopy. The majority of the patients however did not fit into any of the syndromes proposed in the literature. Indeed the validity of both Zieve's syndrome and the "transient stomatocytosis with haemolysis" syndrome is questioned.

# HEPARIN TREATMENT OF DEEP VENOUS THROMBOSIS (DVT) CLINICAL VALUES OF HEPARIN ASSAYS

H A Holm, U Abildgaard and Chr Bjerkelund  
Med Dep A, Aker Hospital, Oslo 5, Norway

In a multi center trial patients with phlebographically verified DVT are given continuous heparin infusion for at least 5 days. Blood samples are drawn daily for determination of heparin by 3 different methods: 1) APTT - a 'global' test reflecting heparin effect on the intrinsic system (Cephotest<sup>R</sup>) 2) Thrombin time and 3) An amidolytic assay for determination of heparin concentration (1) (Coatest<sup>R</sup>). The study is still in progress and this report is preliminary (1 Teien Thromb Res 8 1976).

Of 120 patients admitted to the trial 4 patients have suffered serious bleedings requiring blood transfusion. In one patient an intrathoracic bleeding - probably caused by a thoracocentesis - contributed to a fatal outcome 2 days after onset of heparin therapy. Heparin was in the lower part of therapeutic range as determined by all three assays.

The three non-fatal bleedings had average heparin concentration (amidolytic assay) above therapeutic range (0.2 - 0.7 U/ml). APTT-values were above therapeutic range (>120 sec) two days or more in the non-fatal bleedings.

1/5 of the total material had average heparin concentration above therapeutic range and 1/4 had two or more APTT-values above therapeutic range.

Thrombin time in patients with bleedings did not differ significantly from the rest of the material.

Thrombocytopenia has been reported in a great proportion of patients receiving heparin prepared from bovine lung (2). In our study all patients are treated with heparin prepared from porcine mucosa (Heparin Nyco). Thrombocytopenia has been recorded in only one patient. This patient died from pulmonary embolism without signs of bleeding. Other hemostatic parameters indicated consumption coagulopathy (DIC) (2 Bell Ann Intern Med 1976 85 155-160).

We conclude that thrombocytopenia does not seem to represent a major problem with the type of heparin used in this study.

Our preliminary results indicate that amidolytic assay and APTT may be of value in monitoring heparin therapy by decreasing the risk of bleeding complications. Thrombin time assay does not seem to have this property.

## CLINICAL SIGNIFICANCE OF ANTIFACTOR Xa ASSAY

O R Oddegård and U Abildgaard, Med Dep A,  
Aker Hospital, Oslo S, Norway

Earlier studies have shown that antithrombin III probably is the main naturally occurring inhibitor of activated blood coagulation factor X ("antifactor Xa"). Using the factor Xa susceptible chromogenic substrate Bz Ile Glu Gly Arg pNA (S-2222) (1) we have developed an antifactor Xa assay with higher accuracy than conventional antifactor Xa assays.

Using this assay in a clinical material (n = 98) subnormal values were found in the following clinical conditions

- |   |  |          |
|---|--|----------|
| 1 | Hereditary trombophilia                | (n = 8)  |
| 2 | Disseminated intravascular coagulation | (n = 1)  |
| 3 | Liver cirrhosis                        | (n = 9)  |
| 4 | Deep vein thrombosis<br>some patients  | (n = 32) |

In these patients there was a close correlation between the antifactor Xa values and the antithrombin III values.

In three out of 15 individuals with haemophilia the antifactor Xa values were above that found in the reference material (n = 88). This is possibly due to acquired Xa inhibitors developing as a result of multiple transfusions.

# A PROSPECTIVE STUDY OF STREPTOKINASE AND HEPARIN IN THE TREATMENT OF DEEP VEIN THROMBOSIS

H. Arnesen, A. Heilo, E. Jakobsen, B. Ly and E. Skaga  
Medical Department IX and Department of Radiology,  
Ullevål Hospital, University Clinic, Oslo, Norway

In a prospective trial 42 medical patients with a history of deep vein thrombosis of less than five days were allocated at random to treatment with streptokinase or heparin. Only patients with extensive thromboses were included. Streptokinase was given in a loading dose of 250 000 IU and a maintenance dose of 100 000 IU/hour for 4 days as a mean. Heparin was given in a loading dose of 15 000 IU and a maintenance dose of 20 000 - 50 000 IU/day.

The therapeutic results were evaluated by phlebography. Significant thrombolysis occurred in 71.4 % of 21 patients treated with streptokinase and in 23.8 % of 21 patients treated with heparin. Using the  $\chi^2$ -test for overall association this difference was statistically highly significant ( $p < 0.002$ ). Three patients in each treatment group experienced major bleeding, two in each group requiring blood transfusion. Minor bleeding and slight rise in temperature were encountered more often in the streptokinase than in the heparin group.

It is concluded that patients with acute deep vein thrombosis with proximal extension of the thrombus beyond the calf veins should be offered a therapeutic trial with streptokinase.

**CLINICAL SIGNIFICANCE OF ANTIFACTOR Xa ASSAY**  
 O R Odegård and U Abildgaard, Med Dep A,  
Aker Hospital, Oslo 5, Norway

Earlier studies have shown that antithrombin III probably is the main naturally occurring inhibitor of activated blood coagulation factor X ("antifactor Xa") Using the factor Xa susceptible chromogenic substrate B Ile Glu Gly Arg pNA (S 2222) (1) we have developed an antifactor Xa assay with higher accuracy than conventional antifactor Xa assays

Using this assay in a clinical material (n = 98) subnormal values were found in the following clinical conditions

- |   |   |          |
|---|---|----------|
| 1 | Hereditary trombophilia                   | (n = 8)  |
| 2 | Disseminated intravascular<br>coagulation | (n = 1)  |
| 3 | Liver cirrhosis                           | (n = 9)  |
| 4 | Deep vein thrombosis<br>some patients     | (n = 32) |

In these patients there was a close correlation between the antifactor Xa values and the antithrombin III values

In three out of 15 individuals with haemophilia the antifactor Xa values were above that found in the reference material (n = 88) This is possibly due to acquired Xa inhibitors developing as a result of multiple transfusions

# A PROSPECTIVE STUDY OF STREPTOKINASE AND HEPARIN IN THE TREATMENT OF DEEP VEIN THROMBOSIS

H. Arnesen, A. Heilo, E. Jakobson, B. Ly and E. Skaga  
Medical Department IX and Department of Radiology,  
Ullevål Hospital, University Clinic, Oslo, Norway

In a prospective trial, 42 medical patients with a history of deep vein thrombosis of less than five days were allocated at random to treatment with streptokinase or heparin. Only patients with extensive thromboses were included. Streptokinase was given in a loading dose of 250 000 IU and a maintenance dose of 100 000 IU/hour for 4 days as a mean. Heparin was given in a loading dose of 15 000 IU and a maintenance dose of 20 000 - 50 000 IU/day.

The therapeutic results were evaluated by phlebography. Significant thrombolysis occurred in 71.4 % of 21 patients treated with streptokinase and in 23.8 % of 21 patients treated with heparin. Using the  $\chi^2$ -test for overall association, this difference was statistically highly significant ( $p < 0.002$ ). Three patients in each treatment group experienced major bleeding, two in each group requiring blood transfusion. Minor bleeding and slight rise in temperature were encountered more often in the streptokinase than in the heparin group.

It is concluded that patients with acute deep vein thrombosis with proximal extension of the thrombus beyond the calf veins should be offered a therapeutic trial with streptokinase.

**CLINICAL SIGNIFICANCE OF ANTIFACTOR Xa ASSAY**  
O R Odegård and U Abildgaard, Med Dep A,  
Aker Hospital, Oslo 5, Norway

Earlier studies have shown that antithrombin III probably is the main naturally occurring inhibitor of activated blood coagulation factor X ("antifactor Xa"). Using the factor Xa susceptible chromogenic substrate Bz Ile Glu Gly Arg-pNA (S-2222) (1) we have developed an antifactor Xa assay with higher accuracy than conventional antifactor Xa assays.

Using this assay in a clinical material (n = 98) subnormal values were found in the following clinical conditions

- |   |  |          |
|---|--|----------|
| 1 | Hereditary trombophilia                | (n = 8)  |
| 2 | Disseminated intravascular coagulation | (n = 1)  |
| 3 | Liver cirrhosis                        | (n = 9)  |
| 4 | Deep vein thrombosis<br>some patients  | (n = 32) |

In these patients there was a close correlation between the antifactor Xa values and the antithrombin III values.

In three out of 15 individuals with haemophilia the antifactor Xa values were above that found in the reference material (n = 88). This is possibly due to acquired Xa inhibitors developing as a result of multiple transfusions.

1 Aurell L et al Thromb Res 11 595 1977



# THE PROGNOSTIC VALUE OF LOW LEVEL EXERCISE TEST AFTER ACUTE MYOCARDIAL INFARCTION

H Hämäläinen, V Kallio and I Vuori,

Rehabilitation Research Centre of the Social Insurance Institution, Turku, Finland

Ninety-six male patients (mean age 53.2 years) performed a bicycle exercise test with heart rate 110/min as breaking point four weeks after acute myocardial infarction. No complications occurred. For the two first postinfarction years the prognosis of the 32 patients who attained more than 40 watts without cardiac symptoms (group >40 W) was better in terms of cardiovascular mortality: 1 death (3%) compared to 11 deaths (17%) in the 64 patients whose exercise tolerance was limited by cardiac symptoms or manifestations of cardiac dysfunction or whose peak work load was 40 watts or less. Because of the small numbers the difference in mortality was not statistically significant; however, there was no difference in the reinfarction rate: 13% in each group. The rate of previous infarction (9% versus 25%,  $p < 0.05$ ), of cardiac arrhythmias during hospital phase (20% versus 38%,  $p < 0.05$ ) and of malignant arrhythmias (classes 3-5 in low classification) during or after the exercise test (N.S.) was smaller in the > 40 watts group compared to the rest of the patients. The age or the severity of infarction as evidenced by the values of ASAT, LD and relative heart volume and by the rate of myocardial insufficiency during the hospital phase did not show statistically significant differences between the groups. When all the patients alive ( $n = 84$ ) and dead ( $n = 12$ ) during the two years following-up were compared, a statistically highly significant difference in the rate of malignant arrhythmias (11% versus 50%,  $p < 0.001$ ) during or after the exercise test was found. Thus high incidence of malignant arrhythmias in exercise test seemed in this material to be connected with poor prognosis. An early low level exercise test may be a useful tool to discover part of the arrhythmias thus enabling the start of vigorous treatment leading to an eventually improved prognosis.

# INTRAVENOUS DISOPYRAMIDE IN THE CONVERSION OF SUPRAVENTRICULAR ARRHYTHMIAS INTO SINUS RHYTHM

P. V. Luoma, P. A. Kujala and J. T. Takkinen,

Department of Internal Medicine University of Oulu, Oulu, Finland

Cardiac arrhythmias often constitute a very important therapeutic problem that must be treated effectively. Disopyramide is an antiarrhythmic agent that is structurally unrelated to any of the conventional antiarrhythmic compounds. In the present trial we studied the usefulness of intravenous disopyramide in the conversion of supraventricular arrhythmias into sinus rhythm. Fifty seven hospitalized patients without manifest cardiac decompensation were treated on 72 occasions for acute or recent atrial fibrillation or flutter or for supraventricular tachycardia. Patients weighing 70 kg or less received 100 mg disopyramide phosphate and patients over 70 kg 150 mg of this drug by intravenous infusion over a 5 minute period unless the desired effect occurred earlier. The over all success rate in the treatment of 53 cases of atrial fibrillation or flutter was 42 per cent. The duration of atrial fibrillation significantly affected the efficacy of disopyramide. Atrial fibrillation or flutter that had lasted less than 24 hours was treated successfully in 55 per cent of cases. The over all success rate in the treatment of 19 cases of supraventricular tachycardia was 68 per cent.

Disopyramide had no significant effect on blood pressure and no serious side effects were seen. In patients with atrial fibrillation or flutter in which the arrhythmia was not converted into sinus rhythm disopyramide produced an increase in heart rate. The main subjective complaint of the patients was dryness of the mouth that can be attributed to the anticholinergic effect of the drug. It occurred in five out of 72 cases.

In the indications and the dose regimen employed intravenous disopyramide appears to be very useful of rapid action and well tolerated.

# THE PROGNOSTIC VALUE OF LOW LEVEL EXERCISE TEST AFTER ACUTE MYOCARDIAL INFARCTION

H Hämmäläinen, V Kallio and I Vuori,

Rehabilitation Research Centre of the Social Insurance Institution, Turku, Finland

Ninety-six male patients (mean age 53.2 years) performed a bicycle exercise test with heart rate 110/min as breaking point four weeks after acute myocardial infarction. No complications occurred. For the two first postinfarction years, the prognosis of the 32 patients who attained more than 40 watts without cardiac symptoms (group >40 W) was better in terms of cardiovascular mortality: 1 death (3%) compared to 11 deaths (17%) in the 64 patients whose exercise tolerance was limited by cardiac symptoms or manifestations of cardiac dysfunction or whose peak work load was 40 watts or less. Because of the small numbers the difference in mortality was not statistically significant; however, there was no difference in the reinfarction rate: 13% in each group. The rate of previous infarction (9% versus 25%,  $p < 0.05$ ), of cardiac arrhythmias during hospital phase (20% versus 38%,  $p < 0.05$ ) and of malignant arrhythmias (classes 3-5 in low classification) during or after the exercise test (N.S.) was smaller in the > 40 watts group compared to the rest of the patients. The age or the severity of infarction as evidenced by the values of ASAT, LD and relative heart volume and by the rate of myocardial insufficiency during the hospital phase did not show statistically significant differences between the groups. When all the patients alive ( $n = 84$ ) and dead ( $n = 12$ ) during the two years following-up were compared, a statistically highly significant difference in the rate of malignant arrhythmias (11% versus 50%,  $p < 0.001$ ) during or after the exercise test was found. Thus high incidence of malignant arrhythmias in exercise test seemed in this material to be connected with poor prognosis. An early low level exercise test may be a useful tool to discover part of the arrhythmias thus enabling the start of vigorous treatment leading to an eventually improved prognosis.

# PROGNOSTIC INDEX FOR EARLY DISCHARGE IN ACUTE MYOCARDIAL INFARCTION

E B Madsen, S Rasmussen and T L Svendsen,  
Cardiological Department, Glostrup Hospital, Denmark

For the purpose of selecting patients with acute myocardial infarction (AMI) for early discharge from hospital 332 patients monitored for at least 21 days in a coronary care unit were studied. A new multivariate regression analysis with the survival time as the prognostic end point was utilized (Cox model).

The prognostic variables occurring in the first 5 days of admission were age, sex, localization of AMI, aspartat aminotransferase (ASAT) maximum and area values, lactic dehydrogenase (LHD) maximum value, congestive heart failure, acute pulmonary oedema, cardiogenic shock, cardiac arrest, ventricular or supraventricular tachycardia, ventricular premature beats, atrioventricular block of second or third degree, nodal rhythm, bradycardia, atrial fibrillation and bundle branch block.

Only 4 variables made a significant contribution to the prognosis during the rest of the admission: congestive heart failure (HF), cardiogenic shock (CS), atrioventricular block (AV) and age.

The prognostic index for an individual patient could be calculated by inserting the relevant prognostic variables in the following equation:

$$S = 0.516 \times \begin{bmatrix} 0 & HF \\ 1 & HF \end{bmatrix} + 0 \times \begin{bmatrix} 0 & CS \\ 1 & CS \end{bmatrix} + 2 \times \begin{bmatrix} 0 & AV \\ 1 & AV \end{bmatrix} + 0.03 \times \text{age}$$

The chance of survival of an individual patient ( $p_i$ ) with index  $S$  in relation to the whole group of patients ( $P_0$ ) on different days after the fifth day was  $p_i = P_0 \exp S$ .

The more negative  $S$  the better the prognosis. The correlation coefficient between prognostic index  $S$  and survival time was 0.5. With increasing index from 1 to 3.5 the probability of surviving the 1st day decreased from 98.7% to 9.1%.

Individuals eligible for early discharge could be proposed on the basis of this prognostic index. With a risk of dying from the discharge to day 30 below 5% patients with  $S$  below 0.3 could be discharged at day 6, with  $S$  below 0.3 at day 9, with  $S$  below 0.1 at day 1, with  $S$  below 0 at day 15, and  $S$  below 0.4 at day 18.

This model is now tested on a new larger group of patients.

# LONG-TERM PROGNOSIS AFTER SURGICAL CORRECTION OF COARCTATION OF THE AORTA

K. Forfang, H. Rostad and S. Sørland,  
Rikshospitalet, Oslo, Norway

Up to 1973 356 patients were operated on for coarctation of the aorta in our hospital. There were 13 operative deaths (3.7%). A follow-up study was performed in the years 1975 to 1977: mean follow-up period 12 years (range 2 to 28 years). Of the 305 survivors, 301 answered a questionnaire on subjective symptoms and in 294 cases results from a physical examination were obtained. Further examinations were performed in patients with symptoms and/or abnormal findings.

At follow-up 70.8% felt completely well without symptoms, 26.2% were slightly disabled, whereas 3% were severely disabled. Hypertension was found in 51.2% of the patients aged > 13 years at operation, as compared to 28.6% in the younger age group. Recoarctation was found in 30 patients, the incidence being highest among those who were operated on under 3 years of age. Aortic valve disease was present in 31 patients, 29 of the 38 late deaths were caused by cardiovascular disease, 4 of whom by dissecting aneurysm of the ascending aorta. 12 patients died suddenly and unexpectedly. At the follow-up aneurysm of the ascending aorta was detected in 4 patients with postoperative hypertension. Bacterial endocarditis had occurred in 4 patients, with one death.

Both before and after coarctectomy prophylaxis against endocarditis should be given. Life-long follow up with a view to recoarctation, hypertension and aortic valve disease is needed in all patients. Postoperative angiographic examination of the aorta is recommended.

# PROGNOSTIC INDEX FOR EARLY DISCHARGE IN ACUTE MYOCARDIAL INFARCTION

E B Madsen, S Rasmussen and T L Svendsen,  
Cardiological Department, Glostrup Hospital, Denmark

For the purpose of selecting patients with acute myocardial infarction (AMI) for early discharge from hospital 332 patients monitored for at least 21 days in coronary care unit were studied. A new multivariate regression analysis with the survival time as the prognostic end point was utilized (Cox model).

The prognostic variables occurring in the first 5 days of admission were age, sex, localization of AMI, aspartate aminotransferase (ASAT) maximum and area values, lactic dehydrogenase (LHD) maximum value, congestive heart failure, acute pulmonary oedema, cardiogenic shock, cardiac arrest, ventricular or supraventricular tachycardia, ventricular premature beats, atrioventricular block of second or third degree, nodal rhythm, bradycardia, atrial fibrillation and bundle branch block.

Only 4 variables made a significant contribution to the prognosis during the rest of the admission: congestive heart failure (HF), cardiogenic shock (CS), atrioventricular block (AV) and age.

The prognostic index for an individual patient could be calculated by inserting the relevant prognostic variables in the following equation

$$S = 0.5 + 1.6 \times \begin{bmatrix} 0 & HF \\ 1 & HF \end{bmatrix} + 0 \times \begin{bmatrix} 0 & CS \\ 1 & CS \end{bmatrix} + 1 \times \begin{bmatrix} 0 & AV \\ 1 & AV \end{bmatrix} - 0.03 \times \text{age}$$

The chance of survival of an individual patient ( $p_i$ ) with index  $S$  in relation to the whole group of patients ( $P_0$ ) on different days after the fifth day was  $P_i = P_0 \exp S$ . The more negative  $S$  the better the prognosis. The correlation coefficient between prognostic index  $S$  and survival time was 0.5. With increasing index  $S$  and to 3.5 the probability of surviving the 1st day decreased from 98% to 9.7%.

Individualised early discharge could be proposed on the basis of this prognostic index. With a risk of dying from the day of discharge to day 30 below 5% patients with  $S$  below 0.6 could be discharged at day 6, with  $S$  below 0.3 at day 9, with  $S$  below 0.1 at day 1, with  $S$  below 0 at day 15 and  $S$  below 0.4 at day 18.

This model is now tested on a new larger group of patients.

# CARDIAC ARRHYTHMIAS IN PATIENTS WITH ACUTE CEREBROVASCULAR DISEASE

K. Miah, M. Britton, U. de Faire, C. Helmers, C. Ryding and O. P. Wester.

Department of Internal Medicine, Serafimerlasarettet, Stockholm, Sweden

It is well known that cerebral lesions may induce cardiac arrhythmias. However, indications for continuous ECG monitoring in patients with acute Cerebrovascular Disease have not been agreed upon.

In 100 consecutive patients, mean age 73 years, admitted to a medical stroke unit, 24 hour Holter recordings were made as soon as possible after admission. Only 30 per cent of the patients had no previous cardiac disease. 81 patients had cerebral infarction, 8 cerebral hemorrhage, 9 transitory ischemic attack and 2 patients had non defined cerebrovascular disease.

Only 18 patients showed no arrhythmias during the ECG-recording. 23 patients had chronic atrial fibrillation and another 2 paroxysmal atrial fibrillation. Bradycardia was a rare finding. Ventricular ectopic activity was noted in 42 of the 77 patients (55 per cent) without atrial fibrillation. In 10 patients serious forms of ventricular arrhythmias were registered. 3 of these patients had acute myocardial infarction at the time of recording and they all died. Congestive heart failure was a common finding in the rest of these patients.

Corrected QT-interval ( $QT_c$ ) was calculated in 69 patients without atrial fibrillation or Bundle Branch Block.  $QT_c$  was increased in 46 patients (67 per cent). There was no significant association between an increased  $QT_c$  and ectopic ventricular activity.

**Conclusion:** Concomitant heart disease is frequent in patients with cerebrovascular disease. Close observation for cardiac complications, mainly congestive heart failure but also acute myocardial infarction, is necessary and continuous ECG surveillance may be indicated in such high risk patients.

**EVALUATION OF LEFT VENTRICULAR FUNCTION BY ECHOCARDIOGRAPHY**  
**O A. Nesje and K O. Levorstad,**  
Laboratory of Cardiology, Medical Department B and  
Department of Radiology, Rikshospitalet, Oslo, Norway

The non invasive assessment of left ventricular (LV) function by echocardiography (Echo) is of great practical interest to the cardiologist. In the present study the ejection fraction (EF) of the LV i.e. the relationship between stroke volume (SV) and end diastolic volume (EDV)  $EF \% = SV/EDV \times 100$  (normal value  $> 55 \%$ ) was determined by measuring the transverse diameter of the LV during diastole and systole by single beam M mode Echo in 67 adult patients. The results were compared with the EF calculated from LV angiograms (Angio) obtained during catheterization.

In 31 patients with coronary heart disease (CHD) Echo EF (range 32-76 %) related significantly with Angio EF (range 14-82 %) with  $r = 0.73$  and  $p < 0.001$ . Echo tended to overestimate EF in 6 patients with aneurysms of the anterior wall of the LV (range 36-51 %, mean 46 %) compared to EF determined by Angio (range 14-46 %, mean 28 %). When these 6 patients were excluded from the CHD group the statistical relationship increased to  $r = 0.80$ .

In 16 patients with mitral insufficiency Echo EF (range 56-94 %) related significantly with Angio EF (range 40-88 %)  $r = 0.62$   $p < 0.01$ . In 20 patients with mitral stenosis however there was no statistical relationship between Echo EF (range 44-76 %) and Angio EF (range 53-85 %)  $r = 0.20$ .

The study shows that it is possible to assess LV function by Echo in adult patients. Because its sound beam transverses the LV approximately along the minor axis just distal to the mitral valves single beam M mode Echo is not able to demonstrate an aneurysm of the anterior wall of the LV. But even in these patients Echo correctly pointed to an impairment of LV function. The sound beam furthermore crosses the LV in a direction perpendicular to the Angio plane and it is therefore not surprising that the results of the two methods differ when the geometry and the contraction pattern of the LV are altered as in mitral stenosis.



# CARDIAC ARRHYTHMIAS IN PATIENTS WITH ACUTE CEREBROVASCULAR DISEASE

A. Miah, M. Britton, U. de Faire, C. Helmers, C. Ryding and O. P. Wester,  
Department of Internal Medicine, Serafimerlasarettet,  
Stockholm, Sweden

It is well known that cerebral lesions may induce cardiac arrhythmias. However, indications for continuous ECG monitoring in patients with acute Cerebrovascular Disease have not been agreed upon.

In 100 consecutive patients, mean age 73 years, admitted to a medical stroke unit 24 hour Holter recordings were made as soon as possible after admission. Only 30 per cent of the patients had no previous cardiac disease. 81 patients had cerebral infarction, 8 cerebral hemorrhage, 9 transitory ischemic attack and 2 patients had non defined cerebrovascular disease.

Only 18 patients showed no arrhythmias during the ECG-recording. 23 patients had chronic atrial fibrillation and another 2 paroxysmal atrial fibrillation. Bradycardia was a rare finding. Ventricular ectopic activity was noted in 42 of the 77 patients (55 per cent) without atrial fibrillation. In 10 patients serious forms of ventricular arrhythmias were registered. 3 of these patients had acute myocardial infarction at the time of recording and they all died. Congestive heart failure was a common finding in the rest of these patients.

Corrected QT-interval ( $QT_c$ ) was calculated in 69 patients without atrial fibrillation or Bundle Branch Block.  $QT_c$  was increased in 46 patients (67 per cent). There was no significant association between an increased  $QT_c$  and ectopic ventricular activity.

Conclusion: Concomitant heart disease is frequent in patients with cerebrovascular disease. Close observation for cardiac complications, mainly congestive heart failure but also acute myocardial infarction, is necessary and continuous ECG surveillance may be indicated in such high risk patients.

EVALUATION OF LEFT VENTRICULAR FUNCTION BY ECHOCARDIOGRAPHY  
 O A Nesje and K O Levorstad,  
Laboratory of Cardiology, Medical Department B and  
Department of Radiology, Rikshospitalet, Oslo, Norway

The non invasive assessment of left ventricular (LV) function by echocardiography (Echo) is of great practical interest to the cardiologist. In the present study the ejection fraction (EF) of the LV i.e. the relationship between stroke volume (SV) and end-diastolic volume (EDV)  $EF \% = SV/EDV \times 100$  (normal value  $> 55 \%$ ) was determined by measuring the transverse diameter of the LV during diastole and systole by single beam M-mode Echo in 67 adult patients. The results were compared with the EF calculated from LV angiograms (Angio) obtained during catheterisation.

In 31 patients with coronary heart disease (CHD) Echo EF (range 32-76 %) related significantly with Angio EF (range 14-82 %) with  $r = 0.73$  and  $p < 0.001$ . Echo tended to overestimate EF in 6 patients with aneurysms of the anterior wall of the LV (range 36-51 % mean 46 %) compared to EF determined by Angio (range 14-46 % mean 28 %). When these 6 patients were excluded from the CHD group the statistical relationship increased to  $r = 0.80$ .

In 16 patients with mitral insufficiency Echo-EF (range 56-94 %) related significantly with Angio EF (range 40-88 %)  $r = 0.62$   $p < 0.01$ . In 20 patients with mitral stenosis however there was no statistical relationship between Echo EF (range 44-76 %) and Angio-EF (range 53-85 %)  $r = 0.20$ .

The study shows that it is possible to assess LV function by Echo in adult patients. Because its sound beam transverses the LV approximately along the minor axis just distal to the mitral valves single beam M mode Echo is not able to demonstrate an aneurysm of the anterior wall of the LV. But even in these patients Echo correctly pointed to an impairment of LV function. The sound beam furthermore crosses the LV in a direction perpendicular to the ANGIO plane and it is therefore not surprising that the results of the two methods differ when the geometry and the contraction pattern of the LV are altered as in mitral stenosis.

# CARDIAC ARRHYTHMIAS IN PATIENTS WITH ACUTE CEREBROVASCULAR DISEASE

K. Miah, M. Britton, U. de Faire, C. Helmers, C. Ryding and O. P. Wester,  
Department of Internal Medicine, Serafimerlasarettet,  
Stockholm, Sweden

It is well known that cerebral lesions may induce cardiac arrhythmias. However, indications for continuous ECG monitoring in patients with acute Cerebrovascular Disease have not been agreed upon.

In 100 consecutive patients, mean age 73 years, admitted to a medical stroke unit, 24 hour Holter recordings were made as soon as possible after admission. Only 30 per cent of the patients had no previous cardiac disease. 81 patients had cerebral infarction, 1 cerebral hemorrhage, 9 transitory ischemic attack and 2 patients had non defined cerebrovascular disease.

Only 18 patients showed no arrhythmias during the ECG-recording. 23 patients had chronic atrial fibrillation and another 2 paroxysmal atrial fibrillation. Bradycardia was a rare finding. Ventricular ectopic activity was noted in 42 of the 77 patients (55 per cent) without atrial fibrillation. In 10 patients serious forms of ventricular arrhythmias were registered. 3 of these patients had acute myocardial infarction at the time of recording and they all died. Congestive heart failure was a common finding in the rest of these patients.

Corrected QT-interval (QT<sub>c</sub>) was calculated in 69 patients without atrial fibrillation or Bundle Branch Block. QT<sub>c</sub> was increased in 46 patients (67 per cent). There was no significant association between an increased QT<sub>c</sub> and ectopic ventricular activity.

**Conclusion:** Concomitant heart disease is frequent in patients with cerebrovascular disease. Close observation for cardiac complications, mainly congestive heart failure but also acute myocardial infarction, is necessary and continuous ECG surveillance may be indicated in such high risk patients.

# BLOOD PRESSURE DURING THE ACUTE PHASES OF CEREBROVASCULAR DISEASE

U de Faire, M Britton, C Helmers and P O Wester,  
Department of Medicine, Serafimerlasarettet, Stockholm,  
Sweden    Department of Medicine, Regionsjukhuset, Umeå,  
Sweden

The present investigation was carried out to study the reaction of blood pressure during the course of an acute cerebrovascular stroke

In a material of 100 patients 68 women (mean age 74) and 32 men (mean age 71) consecutively admitted to the stroke unit at Serafimerlasarettet in Stockholm blood pressure (BP) was measured every sixth hour during the first three days of hospital stay and every twelfth hour from then on. Patients on anti-hypertensive treatment on admission maintained their medication during the hospital stay. New therapy was not initiated. About one half of the patients (53 %) exhibited a history of hypertension.

On admission mean BP was 177/94 for females and 174/94 for males. Many of them had substantial BP elevations (35 %  $\geq 195/\geq 110$ ). During the first three days of hospital stay there was a gradual decrease in both systolic and diastolic BP but from then on BP levels were relatively constant.

On the fourth day in the unit mean of BP was 161/84 for females and 151/84 for males. The proportion of patients with BP levels  $\geq 195/\geq 110$  now was small (10 % females and 7 % males).

In conclusion our data show that there is a spontaneous regulation of BP elevations in most cases during the acute phase of a cerebrovascular stroke. This must be taken into account when antihypertensive treatment is considered in patients with acute cerebrovascular stroke.

HYGROTON<sup>(R)</sup> IN ESSENTIAL HYPERTENSION EFFECT OF HYGROTON  
ON CARDIAC OUTPUT RENAL PLASMA FLOW, RENIN AND ALDOSTERONE  
D Falch and A Quist Paulsen,  
Hormone- and Isotope Laboratory, Aker Hospital, Oslo, Norway

The effect of chlorthalidone (50 mg/day) on the central and renal circulation plasma renin activity (PRA) and plasma aldosterone (PA) was studied in 11 patients (aged 37-64 years) with essential hypertension using radioisotope techniques

After 4 months of treatment (4M) the changes from the control measurements (C) were for mean arterial blood pressure (MAP) cardiac index (CI) stroke index (SI) total peripheral resistance index (TPRI), body weight (BW) plasma volume (PV) PRA and PA effective renal plasma flow (ERPF) serum sodium (Na) potassium (K) and chloride (Cl) as follows (mean  $\pm$  SEM)

MAP (mmHg)	C	126 $\pm$ 2	ERPF (ml/min m <sup>2</sup> )	C	229 $\pm$ 19
	4M	108 $\pm$ 2*		4M	211 $\pm$ 13
CI (l/min m <sup>2</sup> )	C	3 571 $\pm$ 0 210	Na <sup>+</sup>	C	139 5 $\pm$ 1 7
	4M	3 078 $\pm$ 0 115	(nmol/l)	4M	141 0 $\pm$ 0 9
SI (ml/beat m <sup>2</sup> )	C	55 $\pm$ 3	K <sup>+</sup>	C	3 9 $\pm$ 0 1
	4M	48 $\pm$ 3	(nmol/l)	4M	3 9 $\pm$ 0 1
TPRI (10 <sup>5</sup> N s m <sup>3</sup> )	C	2957 $\pm$ 236	Cl	C	105 6 $\pm$ 1 2
	4M	2843 $\pm$ 140	(mmol/l)	4M	101 8 $\pm$ 0 8
BW (kg)	C	86 7 $\pm$ 3 1	PRA		
	4M	85 0 $\pm$ 3 1	(nmol A <sub>1</sub> /1 h)	4M	0 84 $\pm$ 0 21
PV (ml/cm)	C	20 4 $\pm$ 0 9	PA	C	255 $\pm$ 23
	4M	20 4 $\pm$ 0 9	(pmol/l)	4M	298 $\pm$ 30

\* = <0 05

MAP fell concomitantly with a fall in SI and BW. There were a slight but insignificant decrease in TPRI and in ERPF. PRA increased. K fell while PA increased insignificantly, indicating that the low K counteracted the stimulation of PA by the activated angiotensins. During Saralasin infusion (angiotensin-II blockade) after 4 months of treatment there was a negative correlation ( $r = -0.78$ ) between the change in MAP and PRA - increment during Hygroton treatment, indicating that the activated renin-angiotensin axis counteracted the blood pressure lowering effect of Hygroton.

# INDUCTION AND INHIBITION OF INJURY TO HUMAN ENDOTHELIAL CELLS IN CULTURE MEDIATED BY PLASMA LIPOPROTEINS

T. Henriksen, S. A. Evensen and B. Carlander,

Institute for Surgical Research and Medical Department A, Rikshospitalet, Oslo, Norway

Endothelial cells derived from the vein of human umbilical cords were used in experiments after 3-10 days in culture. Cellular injury was evaluated by use of a  $^{51}\text{Cr}$  release assay and phase contrast microscopy. Injury induced by low density lipoproteins (LDL, d = 1.019-1.063) accelerated  $^{51}\text{Cr}$  release from endothelial cells to culture medium during 48 h in culture if the ratio between LDL cholesterol concentration and the amount of infranatant proteins in the culture medium exceeded a certain figure. Increasing the LDL cholesterol concentrations without changing a normal LDL/infranant protein ratio did not harm the cultured cells. The first morphological signs of injury observed were an increased number of cytoplasmatic ramifications. The cells rounded up and detached from the culture dish. HDL did not injure the cells within physiological concentrations (0.400 ug HDL cholesterol/ml medium). The injurious effect of LDL was not cell specific as normal as well as LDL receptor negative fibroblasts were injured by LDL.

Inhibition of the LDL induced cellular injury by high density lipoproteins (HDL, d = 1.090-1.21) Addition of HDL in amounts to give a physiological ratio between LDL and HDL in the culture medium significantly decreased the injurious effect of LDL. Increasing the LDL/HDL ratio further decreased the protective effect of HDL. When HDL was replaced by human albumin approximately 60 times more serum albumin than HDL (calculated in moles) was necessary to obtain the same protection against LDL induced injury.

ANGIOTENSIN-II BLOCKADE (SARALASIN) IN COMBINATION WITH  
 RENOGRAPHY IN THE DIAGNOSIS OF RENOVASCULAR HYPERTENSION  
 D Falch and N Norman,  
Hormone- and Isotope Laboratory, Aker Hospital, Oslo 5,  
Norway

Saralasin an angiotensin-II analog produced by Eaton Laboratories was kindly given to us for clinical trial. The typical response is a lowering of blood pressure (BP) during i.v. infusion in renin dependant hypertension.

In the daily routine for the diagnosis of renovascular hypertension Saralasin has been used in combination with a quantitative renographic technique (determination of effective renal plasma flow - ERPF) measurement of plasma renin activity (PRA) and plasma aldosterone (PA).

The diagnosis of renovascular hypertension is based on lateralization in renal vein renin activity.

In essential hypertension Saralasin elicits a fall in ERPF, an increase in PA, a transient increase in BP while PRA is unchanged. Except for the response in BP these effects are similar to those of angiotensin-II. In these respects the angiotensin-II analog acts as an agonist.

In renovascular hypertension Saralasin gives a pronounced lateralization and increase in ERPF and renal vein renin activity, increase or fall in PA and a rapid fall in BP. These effects are explained by displacement of angiotensin-II from the receptors by Saralasin.

In conclusion Saralasin is a valuable tool in combination with measurement of ERPF, PRA, PA and BP in the diagnosis of renovascular hypertension.

## METABOLIC C3 STUDIES IN MAN

L. Brinch, P. Teisberg and I. Akesson,  
Med. dept. 7, Ullevål Hospital and Med. dept. A,  
Rikshospitalet, Oslo, Norway

Immune complexes often activate the complement system which can be considered the most important effector pathway of humoral immunity. In certain disease states immune mechanisms may be of pathogenetic importance and this may be reflected by altered metabolism of complement components. We have studied the metabolism of highly purified and biologically active C3. The  $J^{125}$  labelled C3 was injected together with  $J^{125}$  labelled albumin as control protein into 20 normal individuals and a material of patients of different categories. Plasma radioactivity was recorded in samples taken after 10 minutes, 5 hours and thereafter daily for one week. Radioactivity was determined in 24 hour aliquots of urine for the same period of time. Fractional catabolic rates, synthetic rates and half lives were determined on the basis of these data.

We found that different batches of C3 to some extent behaved differently in the initial part of each study and as compared with albumin plasma volume determined by labelled C3 tended to give too high values. The isolated C3 although in its native form by biochemical criteria may partly have undergone conformational changes. The results obtained in the first part of each study should therefore be interpreted with caution. Mathematical and computerized analysis of data from the latter part of each study however yielded rather narrow limits for fractional catabolic rates and half lives in normals and the method may be useful in evaluating immunological activity in disease.



OBESITY IN RELATION TO SMOKING  
A CROSS-SECTIONAL AND LONGITUDINAL STUDY OF WOMEN  
IN GÖTEBORG, SWEDEN

H. Noppa and C. Bengtsson,  
Department of Medicine, University of Göteborg,  
Göteborg, Sweden

The purpose of the present paper is to analyze the effect of smoking on obesity and the effect of cessation of smoking on body weight from quantitative aspects considered to be of special importance for physicians treating and preventing diseases related to cigarette smoking. A random sample of middle-aged women in Göteborg was studied in 1968-69 (participation rate 90.1 %) and re-studied in 1974-75 (participation rate 80.3 %). The women were divided in two age groups 38-46 and 50-60 years. Current smokers were significantly leaner than non-smokers (2.0 kg and 3.5 kg in the respective age groups). Non-smokers and heavy smokers (> 20 cigarettes per day) were significantly heavier than moderate smokers (2.6 kg and 3.2 kg in the respective age groups and 5.4 kg and 1.2 kg in the respective age groups). Heavy smokers consumed alcoholic beverages significantly more often and were significantly less active during leisure time. The women who quit smoking between the two studies gained weight with 3.7 kg on average and the women who started to smoke lost weight with 0.7 kg on average. The never-smokers and the current smokers gained weight on average with 1.1 kg and 1.4 kg respectively. The differences were statistically significant.

# THE INOTROPIC AND ELECTROPHYSIOLOGIC EFFECTS OF DIGITOXIN COMPARED TO DIGOXIN IN THE DOG HEART IN SITU

J P Anlie,

Medical Department B, Rikshospitalet, Oslo, Norway

The effects of a single intravenous dose of digitoxin or digoxin were tested in 27 pentobarbital anaesthetized Labrador dogs for 8 hours. Since 2.0 mg digoxin caused continuous arrhythmias in 2 dogs consistent with earlier findings by Barr et al 1972 the dose 1.0 mg digoxin was compared to 0 mg digitoxin. The inotropic effect was determined by peak  $dp/dt$  from left ventricular pressure curves in 12 dogs. In these dogs and two others the effects on the specialized conducting system and refractoriness in the right atrium and the AV node were measured by His bundle registration and programmed electrical stimulation. Monophasic action potentials (MAP) were obtained from the right ventricle at spontaneous and constant paced heart rate in 13 dogs.

Digitoxin and digoxin caused a rapid increase in contractility 10 min after the injection of the drugs. The median response after 2 min was slightly higher after digoxin but this difference was not significant. The median maximum response was reached after 120 and 90 min with values 102 % and 47 % above control values after digitoxin and digoxin. After that the responses decreased steadily corresponding to the serum elimination phases of the two drugs. The heart rate and AV nodal conduction and refractoriness was initially changed to the same degree by the drugs and these effects reached an early maximum after 10-15 min. From 2-8 hours however digitoxin was significantly more potent in this respect.

The MAP duration of the right ventricle was initially increased to the same extent by the two drugs. These changes disappeared after 30 min and the MAP remained unchanged after 1.0 and 2.0 mg digoxin. After digitoxin the MAP duration was increased 15-20 % 4-8 hours after the injection indicating a late increase in the absolute refractory period of the ventricles.

It is concluded that digitoxin and digoxin cause similar effects on contractility approximately equivalent to the dose. After the distribution of the drugs has occurred the inotropic response is correlated linearly to serum concentrations. By the same inotropic response however differences exist between digitoxin and digoxin's electrophysiologic effects not correlated to serum concentrations. The possible clinical implications of these findings will be discussed.

# DEGENERATIVE LIVER DISEASE AND ENDOCRINE DYSFUNCTION IN PATIENTS WITH PROGRESSIVE CONE DYSTROPHY

I Frøyshov Larsen, E Hansen and K Berg,  
Medical Department A and Department of Ophthalmology,  
Rikshospitalet, Oslo, and Institute of Medical Genetics,  
University of Oslo, Norway

A new syndrome of progressive cone dystrophy (total colour blindness) endocrine dysfunction and liver degeneration has been observed in 7 patients 6 of whom belonged to one kindred with a high degree of consanguinity

The eye-disorder was characterized by a progressive loss of the photopic mechanism

Four of the patients had a degenerative liver disease demonstrated by elevated transaminases unspecific parenchymal degeneration fatty infiltration and isolated liver cell necrosis in the liver biopsies

Different endocrine defects were demonstrated Three patients had repeated abortions and two were probably infertile In two patients a primary hypothyrosis and in another two low normal thyroid function with a protracted TRH (thyrotropin releasing hormone) test response indicating a hypothalamic defect were observed A defect in the ACTH reserve, as tested by Metyrapone<sup>R</sup> was seen in two patients

Diabetes mellitus of the maturity-onset type diabetes of the young was observed in three patients and a fourth had reduced glucose tolerance with further impairment during pregnancy Diabetes was seldom among the relatives Hypertension was observed in the diabetic patients but several relatives also had elevated blood pressure

All the patients except one (the youngest) had a progressive hearing loss in four classified as neurogenous probably cochlear Among the relatives several cases of hearing defects were reported it is therefore difficult to relate this to the syndrome

Enlarged sella turcica were found in three patients, and in one of these an empty sella was demonstrated by surgery

EEG-changes a generalized dysrhythmia with slow activity were recorded in two of the patients

The pathogenesis of this syndrome is unknown All the different lesions suggest a systemic disorder possibly a membrane defect

# PENETRATION OF BENZYL PENICILLIN TO HUMAN TISSUE FLUID IN SUBCUTANEOUS WICKS AND SKIN BLISTERS

K E Hellum and V Lohmann,

Medical Department B, University of Bergen, Bergen, Norway

Tissue fluid suitable for time concentration studies was obtained from 4 healthy adult volunteers by  
a) implantation of a number of subcutaneous wicks on the back using non-traumatic surgical silk sutures and  
b) production of a series of skin blisters on the forearm by application of local suction

Antibiotic penetration to these fluid compartments was followed for 5 hours after an i v bolus injection of 7 mega units of benzyl penicillin (bpc). The concentration of bpc in serum, wick and blister fluid were determined by an agar well diffusion method

In wick fluid concentrations of bpc were maximal after 10 minutes (viz at the first collection) and were equal to serum levels after 20-60 minutes

In the blister fluid a delayed entry of bpc was demonstrated concentrations being maximal between 1-1 hours. Also the concentration in blister fluid was more sustained as compared to wick fluid in which the elimination phase more closely followed that in serum

Due to the small volume wick fluid may reflect the rapid changes in antibiotic concentrations of the interstitial fluid ("shallow compartment"). Skin blisters containing a larger fluid volume have features more typical of a "deep compartment"

The techniques are safe and well tolerated and both types of fluid are useful for pharmacokinetic studies in humans

# A PROSPECTIVE STUDY OF INTOXICATIONS WITH TRICYCLIC ANTIDEPRESSANT AGENTS (TCA)

J Skjold, P Teisberg, J E Bredesen, P A M Lunde,  
Medical Department 7 and Section of Clin Tox Central Lab  
Ullevål Hospital, Oslo, Norway

We have performed a prospective study of all major self-inflicted intoxications with tricyclic antidepressant agents (TCA) admitted to Med Dept 7 Ullevål Hospital in a 12 months period. The study was initiated for two purposes. We wanted to perform a prospective study of certain clinical and laboratory parameters and secondly we wanted to investigate whether treatment with sodiumbicarbonate upon admission to hospital could be of prophylactic value with regard to the development of the well-known cardiac complications to the TCA intoxications. The material consists of 26 patients of which 17 were women. The mean age was 32.6 years. The mean time lag from the probable intake of drug to hospital admission was only 5 hours. The intoxications were clinically generally mild, 6 being comatose and 5 semicomatose. Drug levels measured in the plasma of 11 of the patients reflected this, 7 having levels beneath 1000 ng/ml. The correlation between anamnestic data on drug intake and measured levels in the blood was generally good, the exceptions being the patients where aspiration of large amounts of tablets was performed shortly after intake. We would like to emphasize particularly this point. Most patients come to hospital comparatively shortly after the drug intake and intense gastric aspiration and lavage may prevent a serious intoxication. The patients were acidemic upon admission, the mean blood pH being 7.38. In the group (12) treated with 1000 ml of 1.4 % sodiumbicarbonate, mean pH was raised to 7.45 within one hour. This group maintained a blood pH close to 7.42 from then on. The other group (14) which did not receive bicarbonate had a pH of 7.37 after one hour and 7.40 after 12 hours. Infusion of sodiumbicarbonate did not have any effect on the elimination of the drug as judged from serial measurements of drug plasma levels. Cardiac complications were few and not of a serious nature. Eleven patients had sinus tachycardia (120/min) upon admission. Arrhythmias were recorded in 4 during the course and one patient developed a bundle branch block. These preliminary results do not allow any conclusions with regard to the possible prophylactic effect of sodiumbicarbonate infusions on the development of cardiac complications.

# PENETRATION OF BENZYL PENICILLIN TO HUMAN TISSUE FLUID IN SUBCUTANEOUS WICKS AND SKIN BLISTERS

K B Hellum and V Lehmann,

Medical Department B, University of Bergen, Bergen, Norway

Tissue fluid suitable for time concentration studies was obtained from 4 healthy adult volunteers by  
a) implantation of a number of subcutaneous wicks on the back using non traumatic surgical silk sutures and  
b) production of a series of skin blisters on the forearm by application of local suction

Antibiotic penetration to these fluid compartments was followed for 5 hours after an i v bolus injection of 2 mega units of benzyl penicillin (bpc). The concentration of bpc in serum, wick and blister fluid were determined by an agar well diffusion method

In wick fluid concentrations of bpc were maximal after 10 minutes (viz. at the first collection) and were equal to serum levels after 20-60 minutes

In the blister fluid a delayed entry of bpc was demonstrated concentrations being maximal between 1-1 hours. Also the concentration in blister fluid was more sustained as compared to wick fluid in which the elimination phase more closely followed that in serum

Due to the small volume wick fluid may reflect the rapid changes in antibiotic concentrations of the interstitial fluid (shallow compartment). Skin blisters containing a larger fluid volume have features more typical of a "deep compartment"

The techniques are safe and well tolerated and both types of fluid are useful for pharmacokinetic studies in humans

ADJUVANT CYTOSTATIC CHEMOTHERAPY AFTER MASTECTOMY FOR  
BREAST CANCER - TREATMENT FOR ONE WEEK OR FOR ONE YEAR?  
Report from The Scandinavian Adjuvant Chemotherapy Study  
Group by R Nissen-Meyer,  
Aker sykehus Oslo 5, Norway

Eleven hospitals in Finland Norway and Sweden have since January 1965 studied the effect of one single six-day i v Cyclophosphamide course (total dose 30 mg/kg) given as adjuvans to the conventional treatment of primary breast cancer To 507 patients the first injection was given few hours after mastectomy Their randomized control group included 519 patients In March 1976 this control group had 234 recurrences and 196 deaths the treatment group only 175 recurrences and 146 deaths Computed according to life table methods the differences in percent free of disease and crude survival increased gradually during the first 4 respectively 6 postoperative years and reached a plateau of about 10-11 % which was maintained at least until 10 years after mastectomy The differences mentioned were highly significant, and must be interpreted as an increase in cure rate

The effect was as good in the prognostically most favourable group as in the locally more advanced groups and as good in postmenopausal as in premenopausal cases

The side effects were negligible or mild and of short duration Consequently there is no reason to restrict this simple adjuvant treatment to high-risk cases

In a parallel series where administration of the same adjuvant chemotherapy course was delayed until 2-4 weeks after mastectomy no effect was observed

During the last two years another clinical trial (Bonadonna et al) has attracted much interest It demonstrates that adjuvant chemotherapy continued for one year can increase the diseasefree survival rate during the first 2-3 postoperative years with about 20 % In that trial 12 highdose 3-drug courses were given starting 2-4 weeks after mastectomy The distressing side effects during this year were considerable and it still remains to be seen if the observed effect represents an increased cure rate or only a delay in the appearance of clinically detectable metastases

In order to compare short-term and long-term adjuvant chemotherapy our study group has started a new series where all patients receive one short combination chemotherapy course immediately after mastectomy and one half of the stage II patients continue with such courses for one year

# CORRECTNESS OF BEDSIDE DIAGNOSIS IN CEREBROVASCULAR DISEASE

V. Murray, H. Britton, H. de Faire, C. Holmers & P. O. Koste  
Department of Medicine, Serafimer Hospital, Stockholm  
and Umeå University, Umeå, Sweden

In 142 cases of acute stroke taken into a stroke unit preliminary diagnoses were made by at least one senior and one junior doctor. The diagnoses were based only on the patient's history and the results of physical examination. To evaluate the correctness of these bedside diagnoses the were subsequently compared with the diagnoses established after examinations and a final discussion in each case. Regularly the following investigations had taken place: Spectrophotometry of the spinal fluid, x-ray of the skull, echoencephalography and brain scintigrams. In 47 cases either autopsy or angiography had also been performed.

Totally 61% of the preliminary diagnoses turned out to be correct. In five cases the neurological symptoms were explained by other diseases than stroke: namely myocardial infarction (2), Bell's palsy (1), brain tumour (1) and meningitis (1). The rest of the cases remained cerebrovascular although mistakes were made regarding the subgroup. No special group was consistently over- or underdiagnosed. Among the presumed intracerebral haemorrhages only 26% (5/19) could be verified compared to 78% (52/68) of the suspected thromboses and 66% (17/26) of the emboli. In 19 cases the attack was thought to be transitory and this turned out to be true in 63%.

He also studied if the degree of correctness was correlated to the clinical feeling of certainty. Thus it turned out that when the bedside diagnosis had been considered fairly certain it was correct in 82% whereas it was verified in only 46% when it had been considered probable.

To study if increasing experience gave us greater ability in this type of diagnosing we divided the material in three consecutive parts. There were more mistakes made during the first period than during the second and third but the difference was not statistically significant.

Despite experience great interest and literature studies it thus did not seem possible to establish a type bedside findings.



## VESSEL DAMAGE CAUSED BY TOBACCSMOKING IN HUMANS

I Asmussen,

Department of Obstetrics YA, Rigshospitalet, København, Denmark

Tobaccosmoking is considered one of the major riskfactors in the development of atherosclerosis. The connection between smoking and atherosclerosis have been pointed out by several clinical and epidemiological studies. In animal experiments using exposure studies atherosclerosis as well as the development of atherosclerosis have been demonstrated using hypoxia, carbon monoxide etc. The initial lesions of the vessel wall have been demonstrated using the electron microscope after a perfusion fixation of the vessel.

28 patients were selected for the study. Half of the patients were heavy cigarette smokers with a minimum daily consumption of 10 cigarettes. The controls have never smoked. The patients were healthy normal pregnant women having a normal pregnancy, a normal delivery giving birth to normal children at term. The specimens studied were the umbilical artery, the umbilical vein and the vessels in the placenta villi. Leakage of the endothelial lining, broadening of the basementmembrane, proliferative response of the media myocytes and edema were characteristic findings. The changes in the intima and media could be classified as both a degenerative and a reparative response to the injury. In the placenta a marked decrease in vascularisation was found.

# YERSINIA ENTEROCOLITICA CARDITIS AS A DIFFERENTIAL DIAGNOSIS AND THE PROGNOSIS OF THIS DISEASE

E Agner, J Hannover Larsen and A Leth,  
Medical Department C and The Laboratory of Rheumatic Research, The Copenhagen County Hospitals at Glostrup and at Gentofte, Denmark

Acute carditis in combination with serological signs of acute infection with *Yersinia enterocolitica* (Y ent ) serotype 3 and no other possible aetiology was diagnosed in seven patients at the Copenhagen County Hospitals (population 570 000) during the 2½ year period 01 01 74 01 07 76. The cardinal symptom in all patients was precordial pain. At the same time elevation of ESR and WBC as well as moderate elevation of coronary enzymes was seen in most patients. This fulfilled 2 of WHO's 3 criterias for acute myocardial infarction. The ECG-changes however in all cases were characteristic of acute pericarditis and in most cases the cardiac symptoms were preceded by gastrointestinal or flu like symptoms. The course was uneventful in all patients and all symptoms disappeared in two weeks.

At the follow up examination 1-3 years later (average 1½ year) all seven patients were in physical well being. Two patients however still presented a Y ent serotype 3 titre = 80 and one of these had persisting ECG abnormality.

It is observed that in one half of the patients the aetiology would have been missed had not Y ent titre been measured by routine along with the ASO titre and it is therefore concluded that in the case of suspected carditis or suspected myocardial infarction with a discrepancy between clinic or enzymes and ECG changes the diagnosis Y ent carditis should be considered and Y ent antibody titre measured.

SPIROMETRY IN AN URBAN NORDIC POPULATION AGED 20-70 YEARS  
 A. Gulsvik,  
Department of Lung Diseases, Rikshospitalet, Oslo, Norway

The precision and distribution of spirometric lung function variables in a two-phased stratified sample (560 men and 699 women) of the population of Oslo have been studied with a dry wedge spirometer. The regression of the variables to sex, age, height and smoking habits has been examined in a reference group of 124 males and 140 females.

The vital capacity (VC)-, one second forced expiratory volume ( $FEV_{1.0}$ )- and forced mid-expiratory volume ( $FEF_{25-75}$ ) values have a Gaussian (normal) distribution. The  $FEF_{25-75}$  values show three times larger intrasubject variability and twice as large inter subject variability as the VC and  $FEV_{1.0}$  values. The average difference between mean values estimated for the population of Oslo on one hand and mean values observed in the reference group on the other was 5 % in men and 3 % in women, and the difference increased with age.

When standardized for age, height and smoking habits a difference between men and women in the reference group of 17 % and 13 % was observed for  $FEV_{1.0}$  and  $FEF_{25-75}$  respectively. Stepwise multiple regression analysis yielded a larger negative age regression coefficient for  $FEF_{25-75}$  than  $FEV_{1.0}$ .

The average difference between non-smokers and smokers within the reference group was 3 % for  $FEV_{1.0}$  and 7 % for  $FEF_{25-75}$ .

The dispersion of predicted values for lung function variables from different surveys is considerable. Reference values of VC and  $FEV_{1.0}$  derived from Nordic surveys are, in general, higher than those derived from North American surveys.

# A TEN YEAR PROSPECTIVE STUDY OF RESPIRATORY SYMPTOMS AND PULMONARY FUNCTION IN 50 AND 60 YEAR OLDS

E Agner, L Hagerup, P From Hansen, F Lönberg and W Schroll,

From the Glostrup Population Studies of Men and Women born in 1914 The Copenhagen County Hospital at Glostrup, DK 2600 Glostrup, Denmark

Prevalence of respiratory symptoms in a total unselected population of men and women of one age group (born in 1914), living in a suburb of Copenhagen were registered with a 10 year interval at age 50 and 60 respectively. Simultaneous changes in pulmonary function (VC, FEV<sub>1</sub> and PEF<sub>R</sub>) were registered. In 1964 24 % of the men and 12 % of the women reported cough and/or phlegm for at least three months of the year during the last two years. This combination of answers to the British Medical Research Council Questionnaire on bronchitis has here been designated questionnaire positivity. In 1974 the corresponding figures were 35 % of the men and 24 % of the women. Although more men than women had respiratory symptoms at the entry of the study the incidence in the decennium 50-60 was of the same magnitude in both sexes. Acute exacerbations of phlegm were more frequent in women than in men in both examinations and were statistically related to questionnaire positivity while this was only the case in 50 year old men. The prevalence of dyspnoea did not differ in the two sexes in any of the examinations. Only in men however it was statistically related to questionnaire positivity. Pulmonary function tests of the age of 50 and 60 were well related to questionnaire-positivity. Low values of FEV<sub>1</sub> at the age of 50 and respiratory symptoms appeared to be significant risk factors for death during the decade studied.

The course of symptoms in individuals between age 50 and 60 is described in 4 groups. Questionnaire positivity at both examinations were associated with the lowest pulmonary function at the age of 60 while those with no symptoms at any of the examinations had significantly higher values of FEV<sub>1</sub> and VC at the age of 60. The participants developing cough and/or phlegm as a new symptom between the two surveys showed intermediate values. The ten year difference in FEV<sub>1</sub> as a percent of FEV<sub>1</sub> (50) was in women statistically more pronounced in the group with respiratory symptoms at both surveys than in the group without any symptoms. In the men the same tendency was seen although it was not statistically significant.

SPIROMETRY IN AN URBAN NORDIC POPULATION AGED 20-70 YEARS  
A. Gulsvik,  
Department of Lung Diseases, Rikshospitalet, Oslo, Norway

The precision and distribution of spirometric lung function variables in a two-phased stratified sample (560 men and 699 women) of the population of Oslo have been studied with a dry wedge spirometer. The regression of the variables to sex, age, height and smoking habits has been examined in a reference group of 124 males and 140 females.

The vital capacity (VC) - one second forced expiratory volume ( $FEV_{1.0}$ ) - and forced mid-expiratory volume ( $FEF_{25-75}$ ) values have a Gaussian (normal) distribution. The  $FEF_{25-75}$  values show three times larger intrasubject variability and twice as large inter-subject variability as the VC and  $FEV_{1.0}$  values. The average difference between mean values estimated for the population of Oslo on one hand, and mean values observed in the reference group on the other, was 5 % in men and 3 % in women, and the difference increased with age.

When standardized for age, height and smoking habits a difference between men and women in the reference group of 17 % and 13 % was observed for  $FEV_{1.0}$  and  $FEF_{25-75}$ , respectively. Stepwise multiple regression analysis yielded a larger negative age regression coefficient for  $FEF_{25-75}$  than  $FEV_{1.0}$ .

The average difference between non-smokers and smokers within the reference group was 3 % for  $FEV_{1.0}$  and 7 % for  $FEF_{25-75}$ .

The dispersion of predicted values for lung function variables from different surveys is considerable. Reference values of VC and  $FEV_{1.0}$  derived from Nordic surveys are in general higher than those derived from North American surveys.

## TRIMIPRAMINE IN THE TREATMENT OF GASTRIC ULCER

K. Valnes, J. Hyren and T. Qvigstad,

Medical Department, The Central Hospital of Akershus and  
Medical Department 9, Ullevål Hospital, Oslo, Norway

Forty patients with endoscopically confirmed gastric ulcers completed a double blind study comparing trimipramine with placebo during four weeks treatment. The daily dose of trimipramine was 50 mg given before bedtime. No serious side effects occurred.

After four weeks treatment 12 of the 20 patients receiving trimipramine had endoscopically completely healed ulcers while in the placebo group only 4 of the 20 ulcers were healed ( $p=0.025$ ). With regard to the patients' complaints a distinct and statistically significant improvement was also observed in the patients receiving trimipramine ( $p=0.025$ ).

It is assumed that the previously shown antisecretory effect of the drug together with the sedative and antidepressive effect make trimipramine a valuable drug in the treatment of peptic ulcer disease.

# CHOLEGENIC DIARRHOEA IN THE IRRITABLE COLON SYNDROME

E. Hess Thaysen,

Department of Medical Gastroenterology, Aalborg Regional Hospital, Aalborg, Denmark

The versatile  $^{14}\text{C}$ -cholylglycine assay combining  $^{14}\text{C}$  measurements in breath and stool is the most sensitive routine test presently available for detecting ileal disease and bile acid malabsorption (1,3). In this context it must be emphasized that ingestion of bile acid sequestering agents such as cholestyramine, dietary fibres and antacids containing aluminiumhydroxide can result in a positive assay (stool  $^{14}\text{C}$ ).

In the absence of ileal disease a positive stool test indicating bile acid malabsorption can occur in patients with lactose malabsorption, thyrotoxicosis and truncal vagotomy (but not after Billroth II gastrectomy).

In the course of the study some patients were found in whom their history and the assay suggested cholegenic enteropathy in the absence of conventional ileopathy or any other disorder allied to diarrhoea. These patients originally suspected of refractory nervous diarrhoea were promptly relieved by cholestyramine. The diarrhoea recurred whenever this medication was withdrawn. On reexamination after one to five years persistence of the bile acid waste was evidenced by the assay (2).

- 1) Fromm and Hofmann (1971) Lancet 2 621
- 2) Pedersen and Thaysen (1976) Gut 17 965
- 3) Thaysen (1977) in Clinics in Gastroenterology  
vol 6, p 227

# FIBRE TABLETS AS EFFECTIVE ALTERNATIVE TO WHEAT BRAN IN CHRONIC CONSTIPATION

A Bjørnkleit, O Fausa, A Lovik, S Ritland & E Gjone,  
Medical Department A, Rikshospitalet, Oslo, Norway

Lack of fibre in the diet is suggested to be an important cause of chronic constipation. A fibre supplement in the form of wheat bran is easily available. Some patients find wheat bran untasty and difficult to swallow. However, dietary fibre in tablet form might be better accepted by some of these patients.

We compared the effect of tablets made of fibres from grain and citrus fruits (Dumovital<sup>®</sup> Dumex) to that of wheat bran in 20 chronically constipated patients. The patients were randomly given 20 g wheat bran daily in one two months period and 12 fibre tablets daily in another two months period. They were told to continue their usual diet during the trial and also to take the amount of laxatives they felt need for. The patients were interviewed before the trial and after each two months period. Their stool habits, laxative intake, dyspepsia and abdominal discomfort were registered on a point score scale. The laxative properties of the fibre tablets were shown to be equally good as those of wheat bran. Symptom score for constipation problems for the whole group became more than halved during the trial. Twelve of the 20 patients could during the trial stop the intake of other laxatives. The patients experienced reduction in dyspepsia and abdominal discomfort during the fibre tablet period. After the trial was completed, 8 of the patients said they could prefer to continue with the fibre tablets because the tablets were easier to take than wheat bran. Seven patients preferred wheat bran because they thought it worked better. Three patients judged both preparations as equally good and easy to take. Only patients did not experience any effect from neither fibre tablets nor wheat bran.

The mean intake of dietary crude fibre in this group of patients was calculated from diet histories and was found to be slightly less than that of the average Norwegian diet. We also measured serum-lipids before and at the end of the trial. Serum cholesterol was unchanged whereas serum tri glycerides decreased significantly (20%).

Dietary fibre supplementation is thus of value in the treatment of chronic constipation and fibre tablets are as effective as wheat bran.



# ENZYME ACTIVITIES IN JEJUNAL BIOPSIES IN PATIENTS WITH ATYPICAL COELIAC DISEASE

H J Haga, K J Andersen, H Schjónsbj and D h Skagen  
Medical Department A, University of Bergen, Norway

In patients with coeliac disease there is frequently lack of one or more of the classical symptoms weight loss steatorrhea and diarrhea To see whether the paucity of intestinal symptoms in these atypical forms of coeliac disease could be due to preserved epithelial function of the proximal small intestine (1) we compared the activities of various enzymes in homogenates of jejunal biopsies in 8 patients with typical 9 patients with atypical coeliac disease and in 20 control patients Whereas both groups of patients with coeliac disease had significantly reduced specific activity (U/g protein) of six different brush border enzymes (lactase sucrase maltase alkaline phosphatase,  $\gamma$ -glutamyl transferase and leucin amino peptidase) when compared to the control patients there was no significant difference in the mean specific activity in the two groups of coeliac disease Neither was there any significant difference in the mean activities of plasma membrane enzyme (S-nucleotidase) or lysosomal enzymes (acid phosphatase and N-acetyl- $\beta$ -glucosidase)

The results do not support the hypothesis that the paucity of symptoms in atypical coeliac disease is due to preserved epithelial function of the proximal small intestine

- 1) D B A Silk P J kumar J P h Webb et al  
 Ileal function in patients with untreated coeliac disease Gut 1975 16 261-267

# CARCINOEMBRYONIC ANTIGEN (CEA) IN LIVER DISEASE AND ITS RELATION TO DIFFERENT LIVER FUNCTION TESTS

H. Bell, H. Orjaseter and H. F. Lange,

Kroghstøtten Department of Oslo City Hospital, Oslo and Immunological Department, National Institute of Public Health, Oslo, Norway

Plasma CEA was studied in 165 patients with special emphasis on alcoholic liver diseases. CEA was moderately increased. In 36/109 patients (33 %) with alcoholic liver diseases the CEA value was above 4 ug/l compared with 2/41 (5 %) in the non alcoholic group. In benign biliary disease 3/15 patients (20 %) had CEA above this level. Our normal reference value based on 164 blood donors was 3.5 ug/l (mean + 2SD).

In patients who continued drinking the CEA level remained unchanged over long periods. In contrast to patients who reduced or stopped their alcohol intake. In the latter group CEA dropped from 6.7 to 4.2 ug/l during the first weeks and increased again when the alcohol consumption was resumed. Lack of decrease in patients with elevated CEA values after alcohol withdrawal should arouse suspicion of a possible malignant disease.

A significant correlation was found between CEA level and the level of  $\gamma$ -GT ( $n=66$ ,  $p<0.05$ ) and parallel fluctuations were seen in ASAT, ALAT and alkaline phosphatase.

The frequency of complicating disorders was highest among the alcoholic patients. Of 36 patients with CEA above 5 ug/l, 27 (75 %) had complicating diseases in the respiratory or gastrointestinal tract and 25 (69 %) were smokers. The best correlation between CEA and  $\gamma$ -GT was found in patients with no concomitant disease ( $r=0.55$ ,  $p<0.001$ ,  $n=63$ ). The increase of CEA was greatest in patients with complicating disorders.

Much of the CEA increase in patients with alcoholic liver disease seems to be secondary to respiratory or gastrointestinal tract disorders. This may explain why patients with alcoholic liver disease have elevated plasma CEA more often than patients with other liver affections.

## COMMON INTESTINAL BACTERIA IN ETIOLOGY OF COLON CANCER

T P Störtebecker,

Akerbyvägen 282, Täby, Stockholm, Sweden

The incidence of colon cancer is higher throughout the Western industrialized world than among populations of more primitive and rural conditions (IARC)

The incidence of colon cancer does not run parallel to the incidence of gastric cancer, which contradicts that colon cancer is caused by environmental carcinogens from the food supply

Thus the cause of colon cancer has to be due to an increased production of carcinogens in the contents of the great bowel

In their metabolism microorganisms are able to synthesize polycyclic hydrocarbons and carcinogens (i a Birch & Smith, Ehrensverd)

Both fungi as *Aspergillus flavus* and *Geotrichum candidum* and common intestinal bacteria as *E coli* are potent synthesizers of carcinogens

Colon cancer is common in villous polyps but very rare in flat ones (i a Morson)

A long lasting retention of microorganisms in crypts of villous polyps induces an increased biosynthesis of carcinogens

A chronic constipation so common among people of the Western world may contribute to a high production of carcinogens in the colon

Our most efficacious therapy against colon cancer may be to counteract constipation and to alter the intestinal microflora and by these means we are able to decrease the biosynthesis of carcinogens in the colon

For references see T P Störtebecker Unnecessary Cancer  
Chronic Infections as a Cause of Cancer  
Natur och Kultur Stockholm 1978 pp 256

# CARCINOEMBRYONIC ANTIGEN (CEA) IN LIVER DISEASE AND ITS RELATION TO DIFFERENT LIVER FUNCTION TESTS

H. Bell, H. Orjaszter and H. F. Lange,

Kroghstøtten Department of Oslo City Hospital, Oslo and  
Immunological Department, National Institute of Public  
Health, Oslo, Norway

Plasma CEA was studied in 165 patients with special emphasis on alcoholic liver diseases. CEA was moderately increased. In 36/109 patients (33 %) with alcoholic liver diseases the CEA value was above 4 ug/l compared with 2/41 (5 %) in the non alcoholic group. In benign biliary disease 3/15 patients (20 %) had CEA above this level. Our normal reference value based on 164 blood donors was 3.5 ug/l (mean + 2SD).

In patients who continued drinking the CEA level remained unchanged over long periods in contrast to patients who reduced or stopped their alcohol intake. In the latter group CEA dropped from 6.7 to 4.2 ug/l during the first weeks and increased again when the alcohol consumption was resumed. Lack of decrease in patients with elevated CEA values after alcohol withdrawal should arouse suspicion of a possible malignant disease.

A significant correlation was found between CEA level and the level of  $\gamma$ -GT ( $n=66$ ,  $p<0.02$ ) and parallel fluctuations were seen in ASAT, ALAT and alkaline phosphatase.

The frequency of complicating disorders was highest among the alcoholic patients. Of 36 patients with CEA above 5 ug/l, 27 (75 %) had complicating diseases in the respiratory or gastrointestinal tract and 25 (69 %) were smokers. The best correlation between CEA and  $\gamma$ -GT was found in patients with no concomitant disease ( $r=0.55$ ,  $p<0.001$ ,  $n=63$ ). The increase of CEA was greatest in patients with complicating disorders.

Much of the CEA increase in patients with alcoholic liver disease seems to be secondary to respiratory or gastrointestinal tract disorders. This may explain why patients with alcoholic liver disease have elevated plasma CEA more often than patients with other liver affections.

COMMON INTESTINAL BACTERIA IN ETIOLOGY OF COLON CANCER  
 T P Störtebecker,  
Akerbyvägen 282, Täby, Stockholm, Sweden

The incidence of colon cancer is higher throughout the Western industrialized world than among populations of more primitive and rural conditions (IARC)

The incidence of colon cancer does not run parallel to the incidence of gastric cancer which contradicts that colon cancer is caused by environmental carcinogens from the food supply

Thus the cause of colon cancer has to be due to an increased production of carcinogens in the contents of the great bowel

In their metabolism microorganisms are able to synthesize polycyclic hydrocarbons and carcinogens (i a Birch & Smith Ehrensward)

Both fungi as *Aspergillus flavus* and *Geotrichum candidum*, and common intestinal bacteria as *E coli*, are potent synthesizers of carcinogens

Colon cancer is common in villous polyps but very rare in flat ones (i a Morson)

A long lasting retention of microorganisms in crypts of villous polyps induces an increased biosynthesis of carcinogens

A chronic constipation so common among people of the Western world, may contribute to a high production of carcinogens in the colon

Our most efficacious therapy against colon cancer may be to counteract constipation and to alter the intestinal microflora and by these means we are able to decrease the biosynthesis of carcinogens in the colon

For references see T P Störtebecker Unnecessary Cancer  
 Chronic Infections as a Cause of Cancer  
 Natur och Kultur Stockholm 1978 pp 256

# CARCINOEMBRYONIC ANTIGEN (CEA) IN LIVER DISEASE AND ITS RELATION TO DIFFERENT LIVER FUNCTION TESTS

H. Bell, H. Orjaseter and H. F. Lange,

Kroghstøtten Department of Oslo City Hospital, Oslo and  
Immunological Department, National Institute of Public  
Health, Oslo, Norway

Plasma CEA was studied in 165 patients with special emphasis on alcoholic liver diseases. CEA was moderately increased. In 36/109 patients (33 %) with alcoholic liver diseases the CEA value was above 4 ug/l compared with 2/41 (5 %) in the non alcoholic group. In benign biliary disease 3/15 patients (20 %) had CEA above this level. Our normal reference value based on 164 blood donors was 3.5 ug/l (mean + 2SD).

In patients who continued drinking the CEA level remained unchanged over long period. In contrast to patients who reduced or stopped their alcohol intake. In the latter group CEA dropped from 6.7 to 4.2 ug/l during the first weeks and increased again when the alcohol consumption was resumed. Lack of decrease in patients with elevated CEA values after alcohol withdrawal should arouse suspicion of a possible malignant disease.

A significant correlation was found between CEA level and the level of  $\gamma$ -GT ( $n=66$ ,  $p<0.02$ ) and parallel fluctuations were seen in ASAT, ALAT and alkaline phosphatase.

The frequency of complicating disorders was highest among the alcoholic patients. Of 36 patients with CEA above 5 ug/l, 27 (75 %) had complicating diseases in the respiratory or gastrointestinal tract and 25 (69 %) were smokers. The best correlation between CEA and  $\gamma$ -GT was found in patients with no concomitant disease ( $r=0.55$ ,  $p<0.001$ ,  $n=63$ ). The increase of CEA was greatest in patients with complicating disorders.

Much of the CEA increase in patients with alcoholic liver disease seems to be secondary to respiratory or gastrointestinal tract disorders. This may explain why patients with alcoholic liver disease have elevated plasma CEA more often than patients with other liver affections.

Abildgaard U  
 Agner E  
 Amlie J P  
 Andersen K J  
 Arnesen, H  
 Asmussen I  
 Bell H  
 Bengtsson C  
 Berg K  
 Bjerkelund Chr  
 Bjørneklett A  
 Bredeesen J E  
 Brinch L  
 Britton M  
 Böhmer T  
 Carlander, B  
 Digranes Ø  
 Eie H  
 Elgjo K  
 Evensen S A  
 de Faire U  
 Falch D  
 Fausa O  
 Forfang K  
 Gjone E  
 Gulsvik A  
 Haga H J  
 Hagerup L  
 Hansen E  
 Hansen P From  
 Heilo A  
 Hellum K B  
 Helmers C  
 Henriksen T

Hol R  
 Holm H A  
 Hämäläinen K  
 Jakobsen E  
 Kallio V  
 Kujala P A  
 Lange H F  
 Larsen E Hannover  
 Larsen, I Frøyshov  
 Lehmann V  
 Leth A  
 Levorstad K O  
 Lunde P K M  
 Luoma P V  
 Ly B  
 Lønberg F  
 Løvik A  
 Madsen E B  
 Miah A  
 Murray V  
 Myren J  
 Nesje O A  
 Nissen-Meyer R  
 Noppa H  
 Nordhagen R  
 Norman N  
 Osen K  
 Paulsen A Quist  
 Qvigstad T  
 Rasmussen S  
 Refvem O K  
 Ritland S  
 Rostad B  
 Rostad H  
 Ryding C

Schjønby H  
Schroll M  
Skaga E  
Skagen D W  
Skjoto J  
Störtebecker T P  
Svendsen T L  
Sørland S  
Takkunen J T  
Teisberg P  
Thaysen E Hess  
Valnes K  
Vuori I  
Wester P O  
Wisløff F  
Odegård O R  
Orjaseter H  
Åkesson I





# Acta Medica Scandinavica

Supplomentum 622

## Haemodynamic and endocrinological profile of essential hypertension

*Department of Internal Medicine,  
Zuideriekenhuis, Rotterdam, the Netherlands*

by P. W. de Leeuw, T. L. Kho,  
H. E. Falko, W. H. Birkenhäger and A. Wester



# Acta Medica Scandinavica

Supplementum 622

## Haemodynamic and endocrinological profile of essential hypertension

*Department of Internal Medicine,  
Zuiderziekenhuis, Rotterdam, the Netherlands*

by P W de Leeuw T L Kho  
H E Falke W H Birkenhäger and A Wester

# Acta Medica Scandinavica

originally published as *Nordiskt Medicinskt Arkiv* was founded in 1869 by Professor Axel Key MD. In 1901 (from volume 34) this journal was divided into a medical and a surgical section. Since 1919 (from volume 52) the medical section has been published under the name of *Acta Medica Scandinavica*.

## *Acta Medica Scandinavica*

publishes papers on general medicine mainly from Denmark, Finland, Iceland, Norway, Sweden and the Netherlands. Short preliminary reports (not exceeding two pages) will be published at short notice. The papers are published in English, French or German. *Acta Medica Scandinavica* is published on a non-profit basis.

## *Subscriptions*

to *Acta Medica Scandinavica* (two volumes of six numbers each annually) include free supplements to the current volumes.

## *Subscription Rates*

Per annum = two volumes

In Denmark, Finland, Iceland, Norway, Sweden and the Netherlands Sw. cr. 300 incl. postage. Swedish subscribers add VAT.

Other countries Sw. cr. 345 incl. postage.

## *Chief Editor*

Professor Jan G. Waldenström MD  
*Acta Medica Scandinavica*  
Kungsgatan 54  
S-11135 Stockholm, Sweden

## *Editorial Office*

*Acta Medica Scandinavica*  
Kungsgatan 54  
S-11135 Stockholm, Sweden  
(All correspondence concerning manuscripts and editorial matters)  
Telephone 08/217763

## *Subscription, Distribution and Advertising*

The Almqvist & Wiksell Periodical Company  
Gamla Brogatan 26, Box 62  
S-10120 Stockholm 1, Sweden

## *Printers*

Almqvist & Wiksell  
S-75181 Uppsala, Sweden

**HAEMODYNAMIC AND ENDOCRINOLOGICAL  
PROFILE OF ESSENTIAL HYPERTENSION**

# Acta Medica Scandinavica

originally published as *Nordiskt Medicinskt Arkiv* was founded in 1869 by Professor Axel Key MD. In 1901 (from volume 34) this journal was divided into a medical and a surgical section. Since 1919 (from volume 52) the medical section has been published under the name of *Acta Medica Scandinavica*.

## *Acta Medica Scandinavica*

publishes papers on general medicine mainly from Denmark, Finland, Iceland, Norway, Sweden and the Netherlands. Short preliminary reports (not exceeding two pages) will be published at short notice. The papers are published in English, French or German. *Acta Medica Scandinavica* is published on a non profit basis.

## *Subscriptions*

to *Acta Medica Scandinavica* (two volumes of six numbers each annually) include free supplements to the current volumes.

## *Subscription Rates*

Per annum = two volumes

In Denmark, Finland, Iceland, Norway, Sweden and the Netherlands Sw. cr. 300 incl. postage. Swedish subscribers add VAT.

Other countries Sw. cr. 345 incl. postage.

## *Chief Editor*

Professor Jan G. Waldenström MD  
*Acta Medica Scandinavica*  
Kungsgatan 54  
S-11135 Stockholm, Sweden

## *Editorial Office*

*Acta Medica Scandinavica*  
Kungsgatan 54  
S-11135 Stockholm, Sweden  
(All correspondence concerning manuscripts and editorial matters)  
Telephone 08/217763

## *Subscription, Distribution and Advertising*

The Almqvist & Wiksell Periodical Company  
Gamla Brogatan 26, Box 62  
S-10120 Stockholm 1, Sweden

## *Printers*

Almqvist & Wiksell  
S-75181 Uppsala, Sweden

# Haemodynamic and endocrinological profile of essential hypertension

*Department of Internal Medicine  
Zuiderziekenhuis, Rotterdam the Netherlands*

by P W de Leeuw T L Kho  
H E Falke W H Birkenhäger and A. Wester





## CONTENTS

<b>Part I</b>	
Introduction	9
Methods	11
Selection of patients	11
Blood pressure	11
Cardiac output and total peripheral vascular resistance	12
Glomerular filtration rate and renal haemodynamics	13
Plasma volume	14
Extracellular volume	14
Plasma renin concentration	14
Plasma aldosterone	15
Statistical methods	15
 <b>Part II</b>	
Results	17
A. Relationship with age	18
Mean blood pressure	18
Cardiac output	19
Total peripheral vascular resistance	20
Plasma volume and blood volume	21
Extra cellular volume	21
Glomerular filtration rate	21
Renal plasma flow and renal blood flow	21
Renal vascular resistance	23
Filtration fraction	24
Plasma renin concentration	24
Plasma aldosterone	25



## ABBREVIATIONS

BSA	Body surface area
MAP	Mean arterial pressure
Var	Variability of blood pressure
CO	Cardiac output
Dye	Dye dilution
Imp	Impedance cardiography
HR	Heart rate
SV	Stroke volume
TPR	Total peripheral vascular resistance
PV	Plasma volume
BV	Blood volume
ECV	Extracellular volume
IF	Interstitial fluid
GFR	Glomerular filtration rate
RPF	Renal plasma flow
RBF	Renal blood flow
RVR	Renal vascular resistance
FF	Filtration fraction
PRC	Plasma renin concentration
P aldo	Plasma aldosterone concentration

<b>B Interrelations between variables</b>	26
Systemic haemodynamics	26
Renal haemodynamics	27
Systemic haemodynamics vs. renal haemodynamics	29
Systemic haemodynamics vs. body fluid volumes	31
Renal haemodynamics vs. volumes	31
Renin vs aldosterone	31
Renin vs. systemic haemodynamics	33
Renin vs. renal haemodynamics	33
Renin and aldosterone vs. body fluid volumes	33

### **Part III**

<b>Follow-up study</b>	35
------------------------	----

### **Part IV**

#### **Discussion**

<b>Blood pressure cardiac output and total peripheral vascular resistance</b>	41
---	----

<b>Renal haemodynamics and glomerular filtration</b>	43
--	----

<b>Complications of hypertension myocardial infarction</b>	47
--	----

<b>Summary</b>	49
----------------	----

<b>Acknowledgments</b>	51
------------------------	----

<b>References</b>	53
-------------------	----

<b>Appendix</b>	63
-----------------	----

## ABBREVIATIONS

BSA	Body surface area
MAP	Mean arterial pressure
Var	Variability of blood pressure
CO	Cardiac output
Dye	Dye dilution
Imp	Impedance cardiography
HR	Heart rate
SV	Stroke volume
TPR	Total peripheral vascular resistance
PV	Plasma volume
BV	Blood volume
ECV	Extracellular volume
IF	Interstitial fluid
GFR	Glomerular filtration rate
RPF	Renal plasma flow
RBF	Renal blood flow
RVR	Renal vascular resistance
FF	Filtration fraction
PRC	Plasma renin concentration
P.aldo	Plasma aldosterone concentration

<b>B Interrelations between variables</b>	<b>26</b>
Systemic haemodynamics	26
Renal haemodynamics	27
Systemic haemodynamics vs. renal haemodynamics	29
Systemic haemodynamics vs. body fluid volumes	31
Renal haemodynamics vs. volumes	31
Renin vs aldosterone	31
Renin vs. systemic haemodynamics	33
Renin vs renal haemodynamics	33
Renin and aldosterone vs body fluid volumes	33
 <b>Part III</b>	
<b>Follow-up study</b>	<b>35</b>
 <b>Part IV</b>	
<b>Discussion</b>	
Blood pressure cardiac output and total peripheral vascular resistance	41
Renal haemodynamics and glomerular filtration	43
Complications of hypertension myocardial infarction	47
 Summary	49
Acknowledgments	51
References	53
Appendix	63

## PART I

### Introduction

Blood pressure is normally distributed in the population, the hypertensives being scattered to the right side of the distribution curve. No justification can be found for drawing a dividing line to separate normal and elevated blood pressure. Essential hypertension is viewed upon as a continuous spectrum in which each level of blood pressure ever when obtained by casual reading carries prognostic significance for the development of end-organ disease. Although this is true for epidemiological studies, in small-sized samples it is relevant to define blood pressure levels under controlled conditions. This restriction in particular applies to mild hypertension, a condition on which many physiological studies have been focussed. Mild hypertension may represent a transitional state. The deviation from the normal range in some subjects represents merely a fortuitous finding, whilst in others it proves to be the initial phase of a hypertensive process.

Some studies on so-called borderline hypertensives have been carried out in patients who had been admitted to the investigation after only a single screening and some of these were found to be normotensive during subsequent physiological studies. A run-in period is therefore necessary to come to terms with the condition.

In established hypertension chicken and egg questions often arise as soon as physiological or biochemical studies yield abnormal results. Are such abnormalities contributory factors to the hypertensive state or do they reflect the impact of the increased blood pressure on the organism? Despite this uncertainty such investigation can be rewarding on the strength of the assumption that deviations which are supposed to occur early are likely to be identifiable as factors participating in the elaboration of the hypertensive process, whereas late abnormalities are more likely to result from the hypertensive process itself.

Direct assessment of sequential changes based on follow-up studies can only be carried out in small numbers of patients who do not yet need or refuse effective treatment but who will comply to repeated investigations. The results of such an approach are presented in part III as a finishing touch to our other findings. In the large majority of patient the investigator has to make do with cross-sectional studies, coupled with indirect estimates of the duration of the hypertensive process. The following approach should be considered here.





## PART I

### Introduction

Blood pressure is normally distributed in the population the hypertensives being scattered to the right side of the distribution curve. No justification can be found for drawing a dividing line to separate normal and elevated blood pressure. Essential hypertension is viewed upon as a continuous spectrum in which each level of blood pressure even when obtained by casual reading carries prognostic significance for the development of end-organ disease. Although this is true for epidemiological studies, in small-sized samples it is relevant to define blood pressure levels under controlled conditions. This restriction in particular applies to mild hypertension, a condition on which many physiological studies have been focussed. Mild hypertension may represent a transitional state. The deviation from the normal range in some subjects represents merely a fortuitous finding, whilst in others it proves to be the initial phase of a hypertensive process.

Some studies on so-called borderline hypertensives have been carried out in patients who had been admitted to the investigation after only a single screening and some of these were found to be normotensive during subsequent physiological studies. A run-in period is therefore necessary to come to terms with the condition. In established hypertension chicken- and egg questions often arise as soon as physiological or biochemical studies yield abnormal results. Are such abnormalities contributory factors to the hypertensive state or do they reflect the impact of the increased blood pressure on the organism? Despite this uncertainty such investigations can be rewarding on the strength of the assumption that deviations which are supposed to occur early are likely to be identifiable as factors participating in the elaboration of the hypertensive process, whereas late abnormalities are more likely to result from the hypertensive process itself.

Direct assessment of sequential changes, based on follow-up studies, can only be carried out in small numbers of patients, who do not yet need or refuse effective treatment but who still comply to repeated investigations. The results of such an approach are presented in part III as a finishing touch to our other findings. In the large majority of patients the investigator has to make do with cross-sectional studies coupled with indirect estimates of the duration of the hypertensive process. The following inroad should be considered here.

Firstly a direct estimation of the duration of hypertension is sometimes possible when periodic health examinations have been carried out previously. This criterion at the present state of health care is far from infallible. In the large majority of patients the known duration of hypertension is a mere guess because blood pressure has not been measured or recorded before.

The second best choice in interpreting cross sectional investigations is to use age as a reference frame. It can be conceived that essential hypertension is rooted in early life. Even if such a concept is discarded in favour of the assumption that essential hypertension is a disorder which can arise at any age a strong probability exists that hypertension in young adults has had a short history. Along the same line of reasoning the higher age groups should encompass a relatively large proportion of cases of longstanding hypertension. The use of age as a reference frame is subject to some restrictions. First the relationships with age should be offset against the physiological impact of aging per se.

Secondly it should be borne in mind that early cases keep coming in at any age and that the patterns which could be interpreted as occurring in the later stages will be diluted by a proportion of cases of maturity-onset hypertension.

In order to estimate the influence of these factors the results in the last resort can be compared with those obtained in longitudinal studies. The use of age as a reference frame constitutes the basis of part II A. Another method of appraising the duration of the hypertensive process in cross sectional studies is to select a variable which is known to change *pari passu* with time as a consequence of hypertension. The results of renal function studies have been used as such. It should be borne in mind that this approach is fraught with substantial errors not only because of the erroneous inclusion of cases of unrecognized renal hypertension but also because of the varying severity of the hypertensive process. Nevertheless we have attempted to interrelate different variables in order to keep track of the development of the disease (part II B).

The findings presented in parts II and III will be discussed and compared with the data from other laboratories in part IV in an attempt to establish the physiological biochemical background of the natural history of the disorder.

## Methods

### *Selection of patients*

Patients were selected for the study in the out-patient department. They were considered hypertensive when their blood pressure exceeded 150 mm Hg systolic or 100 mm Hg diastolic during at least three consecutive visits. None of the patients were on antihypertensive therapy during the studies. If they had been treated before, drugs were stopped at least two weeks before admission. The diagnosis of essential hypertension was made after exclusion of known causes of hypertension. The screening protocol consisted of intravenous pyelography, isotope renography and if necessary renal arteriography. None of the patients had proteinuria or excess excretion of vanillyl mandelic acid. When other metabolic diseases such as diabetes, hyperlipidaemia etc. coexisted, subjects were excluded from the study. A further prerequisite for admission was, that hypertension was still benign and uncomplicated, fundal changes with a few exceptions being restricted to grade I or II.

After this initial work-up patients were admitted to a metabolic ward, where they received a standardized diet containing 60 mmol of sodium per day. Potassium intake was not controlled. Usually the patients were in sodium balance on the fourth day of admission. From then on the haemodynamic and endocrinological studies were performed during recumbency and after an overnight fast.

### *Blood pressure*

For 24 hour blood pressure monitoring two types of automatic devices were used. Until 1974 we used a Godart haemotonomograph based on the oscillometric phase shift principle developed by De Dobbeleer (9). After 1974 blood pressure was recorded by the 'Artenosonde' (Roche) which operates through the Doppler effect (107). From the measurements the variability of blood pressure was calculated as the difference between highest and lowest reading expressed as a percentage of the highest value:

$$\left( \frac{P_{\max} - P_{\min}}{P_{\max}} \right) \%$$

During the measurement of cardiac output, intra-arterial pressure was recorded by direct manometry from an indwelling needle and a Statham transducer. Systolic, diastolic and mean pressure were recorded with a Hellige multicardiostat apparatus. For computation of mean blood pressure from indirect recordings the formula of McIntosh (141) was used: mean arterial pressure = diastolic pressure + one third of pulse pressure.

Direct blood pressure values were presented as an average of 70 pulses. Average indirect blood pressure data were calculated from 70 recordings over a 1-hour period during determination of other variables.

Firstly a direct estimation of the duration of hypertension is sometimes possible when periodic health examinations have been carried out previously. This criterion at the present state of health care is far from infallible. In the large majority of patients the known duration of hypertension is a mere guess because blood pressure has not been measured or recorded before.

The second best choice in interpreting cross sectional investigations is to use age as a reference frame. It can be conceived that essential hypertension is rooted in early life. Even if such a concept is discarded in favour of the assumption that essential hypertension is a disorder which can arise at any age a strong probability exists that hypertension in young adults has had a short history. Along the same line of reasoning the higher age groups should encompass a relatively large proportion of cases of longstanding hypertension. The use of age as a reference frame is subject to some restrictions. First the relationships with age should be offset against the physiological impact of aging per se.

Secondly it should be borne in mind that early cases keep coming in at any age and that the patterns which could be interpreted as occurring in the later stages will be diluted by a proportion of cases of maturity-onset hypertension.

In order to estimate the influence of these factors the results in the last resort can be compared with those obtained in longitudinal studies. The use of age as a reference frame constitutes the basis of part II A. Another method of appraising the duration of the hypertensive process in cross-sectional studies is to select a variable which is known to change *par passu* with time as a consequence of hypertension. The results of renal function studies have been used as such. It should be borne in mind that this approach is fraught with substantial errors not only because of the erroneous inclusion of cases of unrecognized renal hypertension but also because of the varying severity of the hypertensive process. Nevertheless we have attempted to interrelate different variables in order to keep track of the development of the disease (part II B).

The findings presented in parts II and III will be discussed and compared with the data from other laboratories in part IV in an attempt to establish the physiological-biochemical background of the natural history of the disorder.

In the last ten years several authors have compared this method with the dye dilution or isotope dilution technique and with a few exceptions good correlations were reported (4 40 41 99 108 121 174) In our hands the relation was acceptable In 15 patients from our series cardiac output was measured by the dye-dilution and the impedance technique simultaneously The values are plotted in fig 1 We have added to the figure values obtained under non-basal conditions (e.g. tilting, saline loading) For the whole group of paired observations there is a weak relationship ( $r = 0.66$   $p < 0.001$ ) There is no significant difference between the regression for the basal and the non-basal determinations. Compared to the dye-dilution method impedance cardiography appears to underestimate cardiac output slightly Total peripheral vascular resistance was calculated from the following formula.

$$T.P.R. (\text{dyn sec. cm}^{-1}) = \frac{M.A.P. (\text{mm Hg})}{C.O. (\text{l/min})} \times 80$$

In those patients where the two methods for cardiac output were used simultaneously the data from the dye-dilution were taken for derivation of peripheral resistance

#### *Glomerular filtration rate and renal haemodynamics*

Renal plasma flow and glomerular filtration rate were estimated by clearance techniques For both measurements a constant infusion was used The infusion clearance was calculated when plasma samples indicated a steady state between infusion and urinary excretion For determining glomerular filtration rate ( $^{57}\text{Co}$ )-cyanocobalamin was used until 1973 ( $^{57}\text{Co}$ )-cyanocobalamin is firmly bound to protein radioactivity of unbound material was determined by subtraction after exhaustive dialysis against 0.9% NaCl After 1973 we changed to inulin clearance inulin being measured by fermentation (197) The methods were compared in a series of 36 subjects (fig 2) and a weak relationship was found ( $r = 0.77$   $p < 0.001$ )

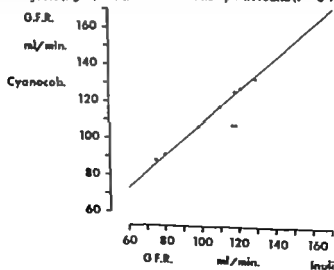


Fig 2 Relationship between glomerular filtration rate measured by cyanocobalamin and inulin (36 subjects 1951-1989;  $r = 0.77$   $p < 0.001$ ).

### Cardiac output and total peripheral vascular resistance

Cardiac output was estimated by the dye dilution technique from 1974 we also used impedance cardiography. After a period during which both methods were applied together to test their congruency the impedance cardiography was used in those patients who were reluctant to undergo arterial puncture.

The dye dilution technique was carried out according to the Stewart Hamilton principle. A known amount of indocyanine green was injected via an antecubital vein while arterial blood was drawn with constant speed by a Harvard Pump from the contralateral brachial artery into a Kipp haemoreflectometer. A direct writing micrograph BD3 (Kipp) recorded the dilution curves. Calibration was performed according to the method of Sparling (177). After correction for re-circulation cardiac output was calculated by planimetric comparison of the circulation curve and the calibration curve.

Impedance cardiography was carried out according to the method of Kubicek (119). Thoracic impedance data were obtained using four electrodes (aluminized tape) and the Minnesota impedance cardiograph (model 304 A).

Two electrodes are placed around the neck, one around the thorax and one around the abdomen. A constant sinusoidal current is applied to the upper and lower electrodes and potential changes are registered from the two middle ones. During end-expiratory breath holding these changes are thought to reflect impedance changes. From the maximum rate of change of impedance stroke volume can be calculated when basal thoracic impedance, ventricular ejection time and distance between the inner electrodes are known.

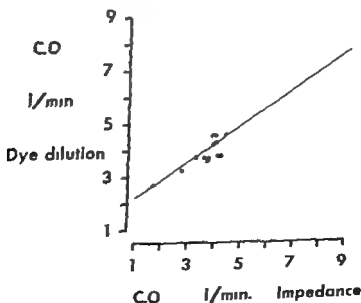


Fig 1 Relationship between cardiac output measured by dye dilution and impedance cardiography at rest and during provocative manoeuvres ( $n = 39$   $y = 1.57 + 0.67x$   $r = 0.66$   $p < 0.001$ )

In the last ten years several authors have compared this method with the dye dilution or isotope dilution technique and with a few exceptions good correlations were reported (4 40 41 99 108 121 174). In our hands the relation was acceptable. In 15 patients from our series cardiac output was measured by the dye-dilution and the impedance technique simultaneously. The values are plotted in fig. 1. We have added to the figure values obtained under non-basal conditions (e.g. tilting, saline loading). For the whole group of paired observations there is a weak relationship ( $r = 0.66$   $p < 0.001$ ). There is no significant difference between the regression for the basal and the non-basal determinations. Compared to the dye-dilution method impedance cardiography appears to underestimate cardiac output slightly. Total peripheral vascular resistance was calculated from the following formula.

$$\text{T.P.R. (dyn sec. cm}^{-2}\text{)} = \frac{\text{M.A.P. (mm Hg)} \times 80}{\text{C.O. (l/min)}}$$

In those patients where the two methods for cardiac output were used simultaneously the data from the dye-dilution were taken for derivation of peripheral resistance.

#### *Glomerular filtration rate and renal haemodynamics*

Renal plasma flow and glomerular filtration rate were estimated by clearance techniques. For both measurements a constant infusion was used. The infusion clearance was calculated when plasma samples indicated a steady state between infusion and urinary excretion. For determining glomerular filtration rate ( $^{57}\text{Co}$ )-cyanocobalamin was used until 1973 ( $^{57}\text{Co}$ )-cyanocobalamin is firmly bound to protein; radioactivity of unbound material was determined by subtraction after exhaustive dialysis against 0.9% NaCl. After 1973 we changed to inulin clearance, inulin being measured by fermentation (197). The methods were compared in a series of 36 subjects (fig. 2) and a weak relationship was found ( $r = 0.77$   $p < 0.001$ ).

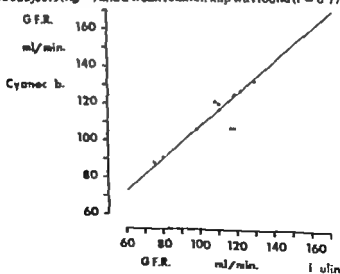


Fig. 2 Relationship between glomerular filtration rate measured by cyanocobalamin and inulin ( $n = 36$ ; 191 0.89;  $r = 0.77$   $p < 0.001$ ).



For determination of renal plasma flow ( $^{125}\text{I}$ )-hippuran was used the infusion clearance was divided by the extraction ratio for hippuran. In early reports from our laboratory a 90% renal extraction was assumed. However, Kolsters (116) has shown that this is an over-estimation since on the average only 74% is extracted. Therefore we have retrieved and recalculated all data from earlier years on this basis. Renal blood flow was calculated from the formula

$$\text{RBF} = \frac{\text{RPF}}{1 - \text{Hi}}$$

where Hi is the venous haematocrit. Renal vascular resistance was then calculated as

$$\text{RVR} (\text{dyn sec cm}^{-5}) = \frac{\text{MAP (mm Hg)}}{\text{RBF (ml/min)}} \times 80,000$$

Filtration fraction was calculated from the quotient  $\frac{\text{GFR}}{\text{RPF}}$

#### *Plasma volume (PV)*

This variable was estimated by determining the dilution of ( $^{125}\text{I}$ )-albumin (RISA) after  $5 \mu\text{Ci}$  was injected intravenously. Blood samples were drawn at 10, 20, 30 and 40 min. Plasma activity was extrapolated to zero time. Blood volume was calculated with the formula

$$\text{BV} = \frac{\text{PV}}{1 - \text{Hi}}$$

#### *Extracellular volume (ECV)*

This variable was estimated by means of radiosulphate. After intravenous injection of  $50 \mu\text{Ci}$  of ( $^{35}\text{S}$ )-sodium sulphate, blood samples were drawn at 10, 60, 90, 120 and 180 min. The zero time value was calculated by semilogarithmic extrapolation.

#### *Plasma renin concentration (PRC)*

Blood samples for renin determination were taken between 09.00 and 10.00 hours. Chilled EDTA-containing tubes were used for collecting the blood, which was centrifuged immediately. Renin was determined according to the method of Skinner (172). An excess of exogenous renin substrate prepared from sheep plasma was added to the specimen. Endogenous renin substrate and angiotensinases were destroyed by dialysis against a buffer solution at pH 3.3. Following incubation with renin substrate prepared from sheep plasma, the angiotensin generated was measured by bio-assay (163, 172) or later by radio-immuno-assay (165, 180). The two methods were frequently compared.

### *Plasma aldosterone*

Blood was collected in the same way as for the renin assay. After purification by paper chromatography, aldosterone was measured by radio-immuno-assay as described by Fraser (65). Recently we started to use the CIS Aldosterone Radio-immuno-assay kit which provides a sensitive and specific determination of aldosterone on dried extracts of plasma samples without chromatography (139).

### *Statistical methods*

Means, standard errors and correlation coefficients were calculated according to standard statistical methods. Regression analysis were carried out using the least squares method.

Differences in means between two groups were assessed by the unpaired Student's *t* test, while the paired *t* test was used for determining changes within groups. A *p*-value of less than 0.05 was accepted as being statistically significant.

For determination of renal plasma flow ( $^{125}\text{I}$ )-hippuran was used the infusion clearance was divided by the extraction ratio for hippuran. In early reports from our laboratory a 90% renal extraction was assumed. However, Kolsters (116) has shown that this is an over-estimation since on the average only 74% is extracted. Therefore we have retrieved and recalculated all data from earlier years on this basis. Renal blood flow was calculated from the formula

$$\text{RBF} = \frac{\text{RPF}}{1-\text{Ht}}$$

where Ht is the venous haematocrit. Renal vascular resistance was then calculated as

$$\text{RVR} (\text{dyn sec cm}^{-5}) = \frac{\text{MAP (mm Hg)}}{\text{RBF (ml/min)}} \times 80\,000$$

Filtration fraction was calculated from the quotient  $\frac{\text{GFR}}{\text{RPF}}$

#### *Plasma volume (PV)*

This variable was estimated by determining the dilution of ( $^{131}\text{I}$ )-albumin (RISA) after 5  $\mu\text{Ci}$  was injected intravenously. Blood samples were drawn at 10, 20, 30 and 40 min. Plasma activity was extrapolated to zero time. Blood volume was calculated with the formula

$$\text{BV} = \frac{\text{PV}}{1-\text{Ht}}$$

#### *Extracellular volume (ECV)*

This variable was estimated by means of radiosulphate. After intravenous injection of 50  $\mu\text{Ci}$  of ( $^{35}\text{S}$ )-sodium sulphate, blood samples were drawn at 30, 60, 90, 120 and 180 min. The zero time value was calculated by semilogarithmic extrapolation.

#### *Plasma renin concentration (PRC)*

Blood samples for renin determination were taken between 09.00 and 10.00 hours. Chilled EDTA-containing tubes were used for collecting the blood, which was centrifuged immediately. Renin was determined according to the method of Skinner (172). An excess of exogenous renin substrate prepared from sheep plasma was added to the specimen. Endogenous renin substrate and angiotensinases were destroyed by dialysis against a buffer solution at pH 3.3. Following incubation with renin substrate prepared from sheep plasma the angiotensin generated was measured by bio-assay (163, 172) or later by radio-immuno-assay (165, 180). The two methods were frequently compared.

## PART II

### Results

#### Cross sectional study

In all 207 patients were selected for the cross-sectional study. There were 123 men (age range 17-73 years) and 84 women (age 19-73 years). The mean age was 45.5 years. Twenty six of these patients underwent follow-up studies for an average period of 4 years (Part III).

Since the entire array of determinations was not carried out in all patients, an account is presented in table 1. The individual data have been recorded in the appendix.

Table 1

Means and standard errors for the various types of investigation

Type of investigation	Number of pat. studied	Results (mean $\pm$ S.E.M.)
Mean blood pressure	173	127 $\pm$ 1 mm Hg
4 hour B.P. recordings (variability)	48	31 $\pm$ 1%
Carotid output by dil. wasp card	100 99	5.64 $\pm$ 0.14 l/min 4.96 $\pm$ 0.14 l/min
Plasma volume	182	2875 $\pm$ 40 ml.
Transcatheter volume	96	11.7 $\pm$ 0.79 l
Cerebral flow rate gamma stud. method	64 99	1.4 $\pm$ 0.2 ml/min 1.08 $\pm$ 0.2 ml/min
Renal plasma flow	184	484 $\pm$ 1 ml/min
Plasma renin concentration	197	9.4 $\pm$ 0.4 ng/hdl h
Plasma aldosterone	91	1.8 $\pm$ 1.3 ng/100 ml



borderline hypertensives as defined by Burkenhäger and Schalekamp (17). When blood pressure is plotted against age a significant positive correlation is obtained (fig. 3  $r = 0.44$   $p < 0.001$ ). The scattergram comprises 173 patients, in 100 of whom blood pressure was measured intra-arterially.

There is no obvious difference in distribution of data obtained from direct and indirect estimations.

Variability of blood pressure was determined in 58 patients and showed a significant inverse relationship with age ( $r = -0.33$   $p < 0.02$ ) as shown in fig. 4.

## 2. Cardiac output

Cardiac output was measured in 159 patients. In 100 of them the dye-dilution technique was used, while in 59 patients the impedance method was applied instead. The relation of cardiac output to age shows a wide scatter, there being no difference between the pattern of the dye-dilution and impedance data (fig. 5). Despite the marked variations, a significant inverse relationship exists between cardiac output and age ( $r = -0.31$   $p < 0.001$ ).

The decline in cardiac output is mainly due to a reduction in stroke volume with age (fig. 6) this relation being significant ( $r = -0.1$   $p < 0.02$ ).

Heart rate and age showed an inverse relationship, but this was not statistically significant ( $r = -0.16$   $0.05 < p < 0.10$ ).

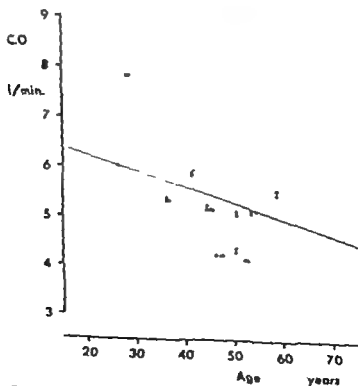


Fig. 5. Relationship between cardiac output measured by dye dilution (closed circles) or impedance cardiography (open circles) and age. For the whole group:  $r = -0.31$   $p < 0.001$ .

## A Relationships with age

In this paragraph we will present the haemodynamic and volume estimations as raw data without conversion to standard body surface area since no differences in B S A could be detected with increasing age

### 1 Mean blood pressure

Although blood pressure was measured in all patients in 34 of them only infrequent readings were obtained at the time of the haemodynamic investigations. These patients were omitted from this section. A minority of the patients was normotensive at the time of the haemodynamic studies they represent the group of

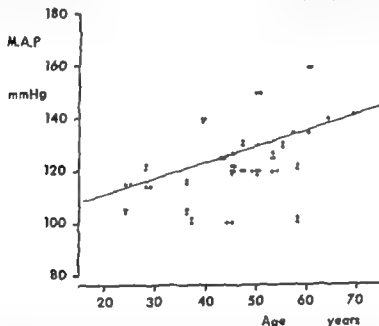


Fig. 3 Relationship between mean arterial pressure and age. Blood pressure was measured intra-arterially (closed circles) or indirectly with an Arteriozone (open circles). Regression analysis yields for the whole group  $y = 98 + 0.63x$  ( $n = 173$   $r = 0.44$   $p < 0.001$ )

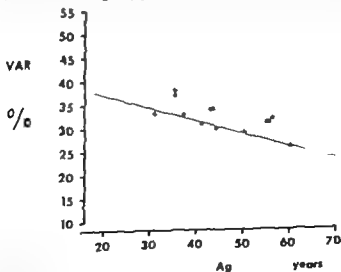


Fig. 4 Relationship between 24-hour variability of blood pressure and age ( $n = 58$   $y = 4 - 0.26x$   $r = -0.33$   $p < 0.07$ )

borderline hypertensives as defined by Wirkenhijger and Schalekamp (17). When blood pressure is plotted against age a significant positive correlation is obtained (fig. 3  $r = 0.44$   $p < 0.001$ ). The scattergram comprises 173 patients, in 100 of whom blood pressure was measured intra-arterially.

There is no obvious difference in distribution of data obtained from direct and indirect estimations.

Variability of blood pressure was determined in 98 patients and showed a significant inverse relationship with age ( $r = -0.33$   $p < 0.01$ ) as shown in fig. 4.

### 7. Cardiac output

Cardiac output was measured in 199 patients. In 100 of them the dye-dilution technique was used while in 99 patients the impedance method was applied instead. The relation of cardiac output to age shows a wide scatter, there being no difference between the pattern of the dye-dilution and impedance data (fig. 5). Despite the marked variations, a significant inverse relationship exists between cardiac output and age ( $r = -0.31$   $p < 0.001$ ).

The decline in cardiac output is mainly due to a reduction in stroke volume with age (fig. 6) this relation being significant ( $r = -0.41$   $p < 0.001$ ).

Heart rate and age showed an inverse relationship but this was not statistically significant ( $r = -0.16$   $0.05 < p < 0.10$ ).

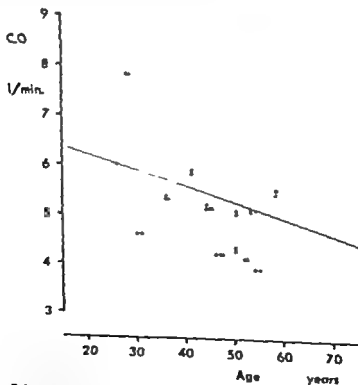


Fig. 5 Relationship between cardiac output measured by dye dilution (closed circles) or impedance cardiography (open circles) and age. For the whole group  $r = -0.31$   $p < 0.001$ .



## A Relationships with age

In this paragraph we will present the haemodynamic and volume estimations as raw data without conversion to standard body surface area since no differences in B S A could be detected with increasing age

### 1 Mean blood pressure

Although blood pressure was measured in all patients in 34 of them only infrequent readings were obtained at the time of the haemodynamic investigations. These patients were omitted from this section. A minority of the patients was normotensive at the time of the haemodynamic studies they represent the group of

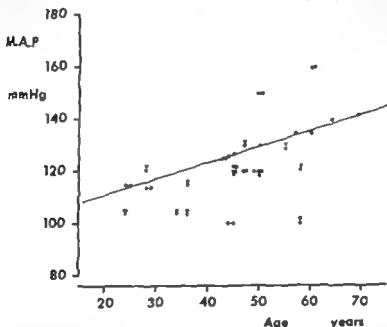


Fig 3 Relationship between mean arterial pressure and age. Blood pressure was measured intra-arterially (closed circles) or indirectly with an Arteriosonde (open circles). Regression analysis yields for the whole group  $y = 98 + 11.63x$  ( $n = 173$   $r = 0.44$   $p < 0.001$ )

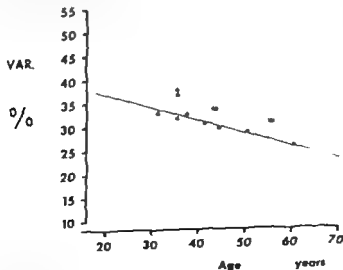


Fig 4 Relationship between 74-hour variability of blood pressure and age ( $n = 18$   $y = 4 - 0.26x$   $r = -0.33$   $p < 0.02$ )

borderline hypertensives as defined by Birkenhager and Schalekamp (17). When blood pressure is plotted against age a significant positive correlation is obtained (fig. 3  $r = 0.44$   $p < 0.001$ ). The scattergram comprises 173 patients in 100 of whom blood pressure was measured intra-arterially.

There is no obvious difference in distribution of data obtained from direct and indirect estimations.

Variability of blood pressure was determined in 58 patients and showed a significant inverse relationship with age ( $r = -0.33$   $p < 0.01$ ) as shown in fig. 4.

## 2. Cardiac output

Cardiac output was measured in 159 patients. In 100 of them the dye-dilution technique was used while in 59 patients the impedance method was applied instead. The relation of cardiac output to age shows a wide scatter, there being no difference between the pattern of the dye-dilution and impedance data (fig. 5). Despite the marked variations, a significant inverse relationship exists between cardiac output and age ( $r = -0.31$   $p < 0.001$ ).

The decline in cardiac output is mainly due to a reduction in stroke volume with age (fig. 6) this relation being significant ( $r = -0.1$   $p < 0.01$ ).

Heart rate and age showed an inverse relationship but this was not statistically significant ( $r = -0.16$   $0.05 < p < 0.10$ ).

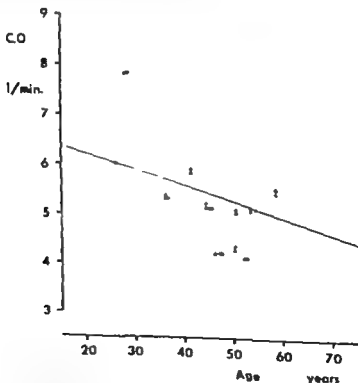


Fig. 5 Relationship between cardiac output measured by dye dilution (closed circles) or impedance cardiography (open circles) and age. For the whole group  $r = -0.31$   $p < 0.001$  ( $n = 159$ ).

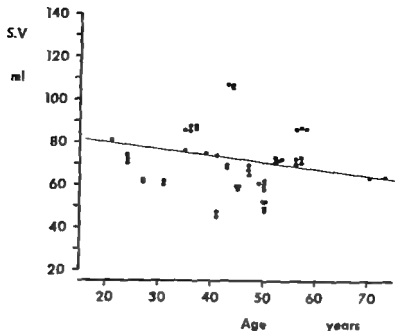


Fig 6 Relationship between stroke volume and age ( $n = 138$   $y = 86 - 0.30x$   $r = -0.21$   $p < 0.07$ )

### 3 Total peripheral vascular resistance

This variable could be calculated for the 159 patients in whom cardiac output was measured. In 100 patients intra arterial blood pressure determinations were available and in the remaining 59 patients the indirect readings from the Arteriosonde were used.

Total peripheral resistance gradually rises with age (fig 7) the relationship being significant ( $r = 0.41$   $p < 0.001$ )

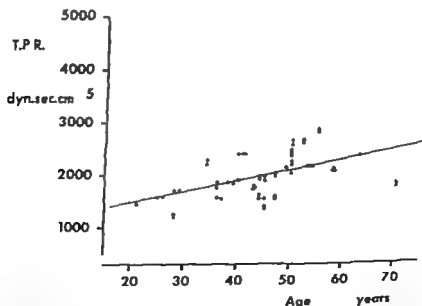


Fig 7 Relationship between calculated total peripheral resistance and age. Closed circles represent calculations from intra-arterial observations open circles represent indirect measurements. For the whole group  $y = 1079 + 1x$  ( $n = 158$   $r = 0.41$   $p < 0.001$ )

#### 4 Plasma volume and blood volume

These variables were measured and calculated in 182 patients. The data are scattered over a wide range and there is no relation between plasma volume or blood volume and age.

#### 5 Extra cellular volume

This variable was measured in 96 patients and showed no relation with age

#### 6 Glomerular filtration rate

In a total of 163 patients glomerular filtration rate was determined in 64 subjects by means of cyanocobalamin clearance and in 99 by inulin clearance. Glomerular filtration rate tends to fall gradually with age (fig. 8  $r = -0.21$   $p < 0.01$ )

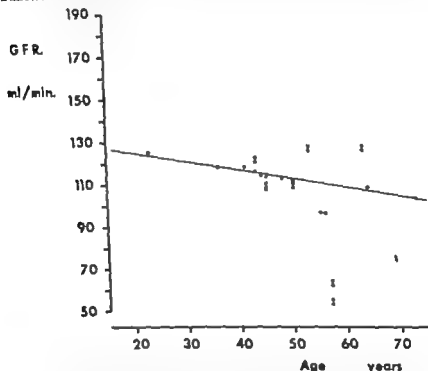


Fig. 8 Relationship between glomerular filtration rate measured by inulin (closed circles) or cyanocobalamin (open circles) and age. Regression analysis yields  $y = 133 - 0.42x$  ( $n = 161$ ,  $r = -0.21$ ,  $p < 0.01$ )

#### 7 Renal plasma flow and renal blood flow

The results are presented in fig. 9. These variables were determined and calculated in 185 subjects. Highly significant inverse relationships are found between renal plasma flow and age ( $r = -0.53$ ,  $p < 0.001$ ) and between renal blood flow and age ( $r = -0.51$ ,  $p < 0.001$ ). It can be inferred from these relations that renal plasma (or blood) flow in the sixth and seventh decade is reduced to about one-half of that at the age of 20 years. The renal fraction of cardiac output also exhibited an inverse relationship with age (fig. 10:  $r = -0.31$ ,  $p < 0.001$ )

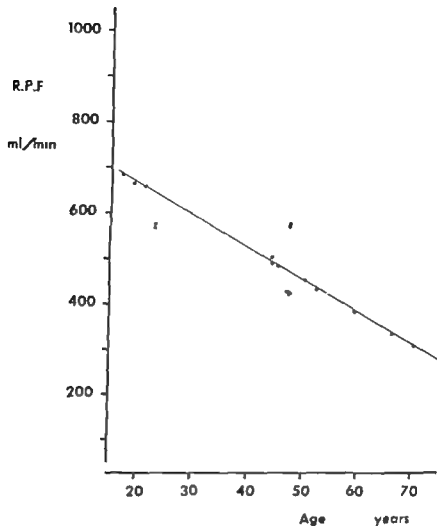


Fig 9 Relationship between renal plasma flow and age ( $n = 185$   $y = 796 - 6.8x$   $r = -0.53$   $p < 0.001$ )

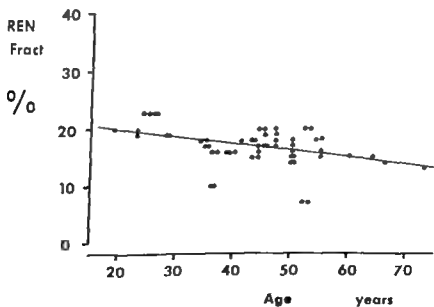


Fig 10 : Relationship between renal fraction and age ( $n = 143$   $y = 23 - 0.14x$   $r = -0.31$   $p < 0.001$ )

## 8 Renal vascular resistance

This variable was calculated for 158 patients. Renal vascular resistance as shown in fig 11 increased with age ( $r = 0.43$   $p < 0.001$ ). There is a suggestion of a curvilinear relationship with a steep increase beyond the age of 40 years. This impression is mainly caused by a small number of patients exhibiting an extremely high R.V.R.

This group was not shown to have particular characteristics apart from the exaggerated increase in R.V.R. Nevertheless we are inclined to consider these patients as a separate group an exception to the rule that R.V.R. increases with age in a linear fashion.

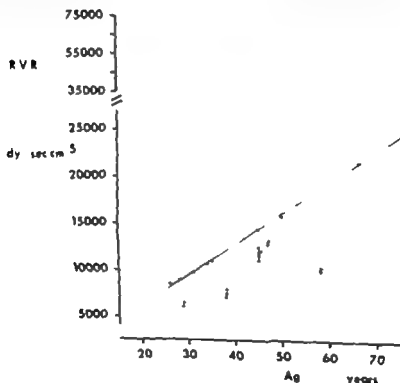


Fig 11 Relationship between calculated renal vascular resistance and age ( $n = 158$ )  
 $r = 0.43$   $p < 0.001$

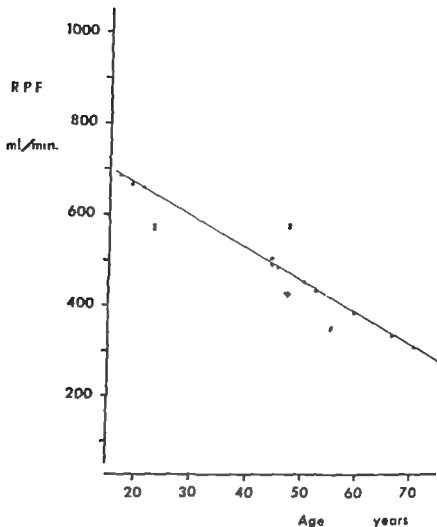


Fig 9 Relationship between renal plasma flow and age ( $n = 185$   $y = 796 - 6.8x$   $r = -0.53$   $p < 0.001$ )

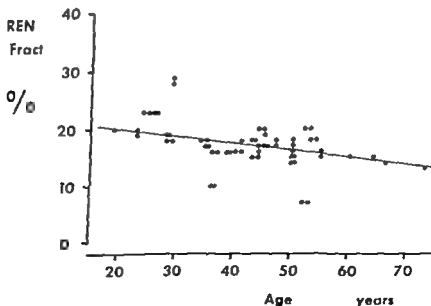


Fig 10 Relationship between renal fraction and age ( $n = 143$   $y = 23 - 0.14x$   $r = -0.31$   $p < 0.001$ )

## 8 Renal vascular resistance

This variable was calculated for 158 patients. Renal vascular resistance as shown in fig. 11 increased with age ( $r = 0.43$   $p < 0.001$ ). There is a suggestion of a curvilinear relationship with a steep increase beyond the age of 50 years. This impression is mainly caused by a small number of patients exhibiting an extremely high R V R.

This group was not shown to have particular characteristics, apart from the exaggerated increase in R V R. Nevertheless we are inclined to consider these patients as a separate group an exception to the rule that R V R increases with age in a linear fashion.

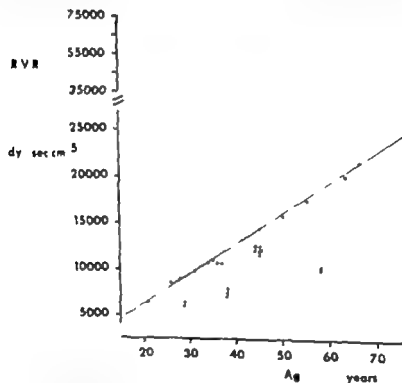


Fig 11 Relationship between calculated renal vascular resistance and age ( $r = 0.43$   $p < 0.001$ )



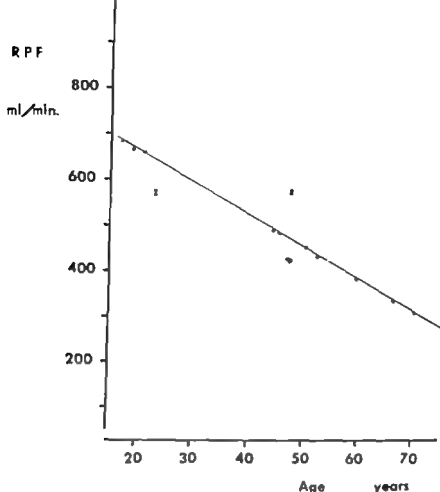


Fig 9 Relationship between renal plasma flow and age ( $n = 185$   $y = 796 - 6.8x$   $r = -0.93$   $p < 0.001$ )

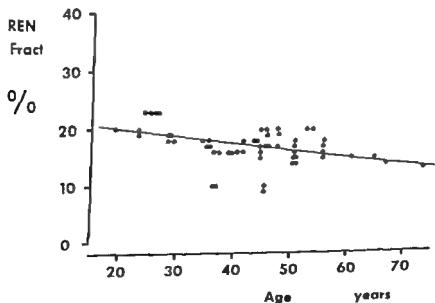


Fig 10 Relationship between renal fraction and age ( $n = 141$   $y = 23 - 0.14x$   $r = -0.31$   $p < 0.001$ )

## 8 Renal vascular resistance

This variable was calculated for 158 patients. Renal vascular resistance as shown in fig. 11 increased with age ( $r = 0.43$   $p < 0.001$ ). There is a suggestion of a curvilinear relationship with a steep increase beyond the age of 50 years. This impression is mainly caused by a small number of patients exhibiting an extremely high R.V.R.

This group was not shown to have particular characteristics apart from the exaggerated increase in R.V.R. Nevertheless we are inclined to consider these patients as a separate group, an exception to the rule that R.V.R. increases with age in a linear fashion.

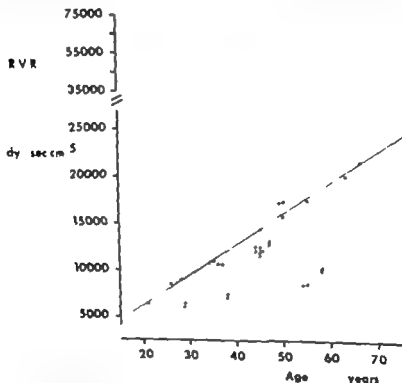


Fig. 11 Relationship between calculated renal vascular resistance and age (n = 158  $y = -722 - 374x - 0.43$   $p < 0.001$ )

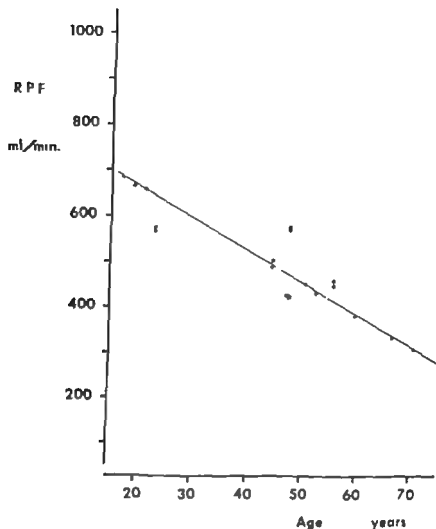


Fig 9 Relationship between renal plasma flow and age ( $n = 185$   $y = 796 - 6.8x$   $r = -0.51$   $p < 0.001$ )

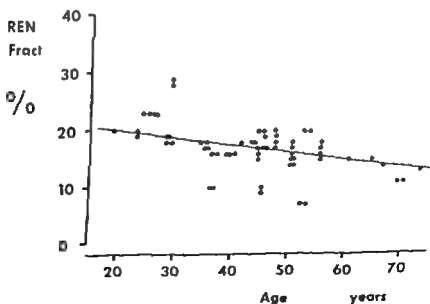


Fig 10 Relationship between renal fraction and age ( $n = 143$   $y = 23 - 0.14x$   $r = -0.31$   $p < 0.001$ )

## 8 Renal vascular resistance

This variable was calculated for 158 patients. Renal vascular resistance, as shown in fig. 11 increased with age ( $r = 0.43$   $p < 0.001$ ). There is a suggestion of a curvilinear relationship with a steep increase beyond the age of 50 years. This impression is mainly caused by a small number of patients exhibiting an extremely high R.V.R.

This group was not shown to have particular characteristics, apart from the exaggerated increase in R.V.R. Nevertheless we are inclined to consider these patients as a separate group, an exception to the rule that R.V.R. increases with age in a linear fashion.

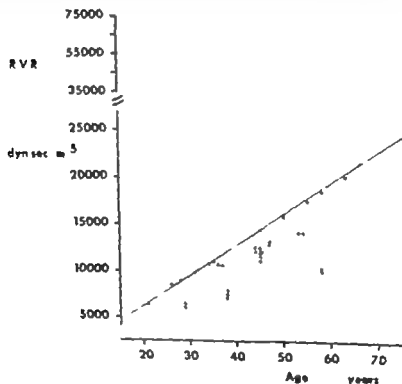


Fig. 11 Relationship between calculated renal vascular resistance and age ( $n = 158$   $y = 124x - 1245$   $r = 0.43$   $p < 0.001$ )

## 9 Filtration fraction

This was calculated in 162 patients. Again there is a positive relation with age (fig 12) which is highly significant ( $r = 0.51$   $p < 0.001$ )

Five patients (2 men and 3 women) had filtration fractions which were extremely high. They all belonged to the group with an abnormally high renal vascular resistance the common denominator being a severely depressed renal plasma flow.

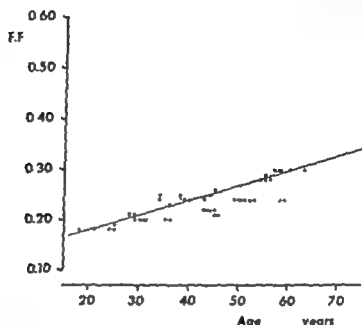


Fig 12 Relationship between filtration fraction and age ( $n = 162$   $y = 0.17 + 0.003x$   $r = 0.51$   $p < 0.001$ )

## 10 Plasma renin concentration

In 10 patients no values for P R C were obtained in most cases this was due to incorrect handling of material at the time of sampling or during the technical procedure. Data from the remaining 197 patients are plotted against age in fig 13. There is a weak tendency for P R C to decline with age until about 50 years ( $r = -0.20$   $p < 0.05$ ) irrespective of changes in glomerular filtration rate. Low renin values are most often encountered between 40 and 60 years. In patients who are older than 50 the relation of P R C with age is no longer present.

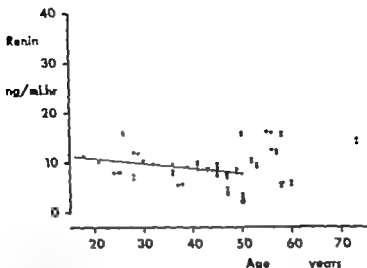
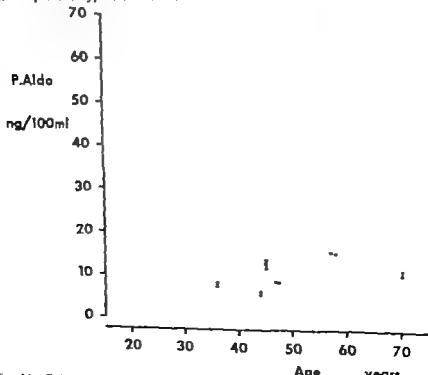


Fig. 13 Relationship between plasma renin concentration and age. A significant correlation is found only in persons below 50 years ( $n = 124$   $y = 12.9 - 0.10x$   $r = -0.20$   $p < 0.05$ )

#### 11 Plasma aldosterone

For the total of 91 observations there is no obvious relation with age (fig. 14). The values for aldosterone are within normal limits in 80 patients. In the remainder with high values we observed no development of clinical hyper-aldosteronism during follow-up in the hypertension clinic.



## 9 Filtration fraction

This was calculated in 162 patients. Again there is a positive relation with age (fig 12) which is highly significant ( $r = 0.51$   $p < 0.001$ )

Five patients (2 men and 3 women) had filtration fractions which were extremely high. They all belonged to the group with an abnormally high renal vascular resistance, the common denominator being a severely depressed renal plasma flow.

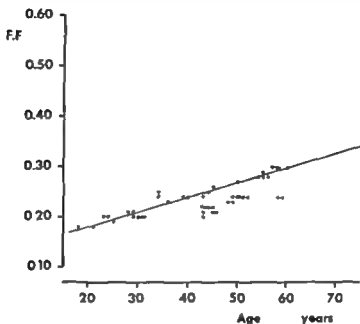


Fig 12 Relationship between filtration fraction and age ( $n = 162$ ,  $y = 0.12 + 0.003x$   $r = 0.51$   $p < 0.001$ )

## 10 Plasma renin concentration

In 10 patients no values for P R C were obtained in most cases this was due to incorrect handling of material at the time of sampling or during the technical procedure. Data from the remaining 197 patients are plotted against age in fig 13. There is a weak tendency for P R C to decline with age until about 50 years ( $r = -0.20$   $p < 0.05$ ) irrespective of changes in glomerular filtration rate. Low renin values are most often encountered between 40 and 60 years. In patients who are older than 50 the relation of P R C with age is no longer present.

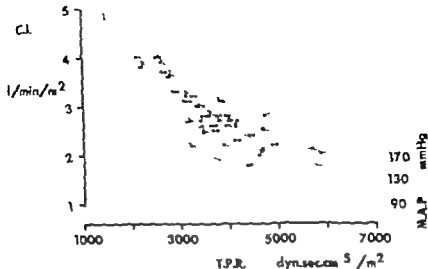


Fig. 16. Nomogram representing the balance between cardiac index, calculated total peripheral resistance and blood pressure

## 2. Renal haemodynamics

Glomerular filtration rate in a particular way is directly related to renal plasma flow (fig. 17). When R.P.F. is lower than around 300 ml/min./m<sup>2</sup> the regression is linear ( $r = 0.62$ ,  $p < 0.001$ ) but above that point the slope of the regression line almost parallels the X-axis which means that at these higher flow rates G.F.R. is practically independent of renal plasma flow. G.F.R. is inversely related to R.V.R. ( $r = -0.57$ ,  $p < 0.001$ ) as shown in fig. 18.

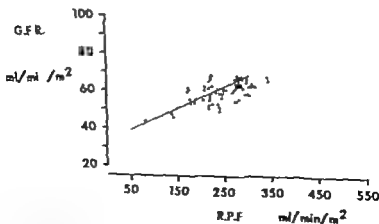


Fig. 17. Relationship between renal plasma flow and glomerular filtration rate. Up to a R.P.F. of about 300 ml/min/m<sup>2</sup> the relation is linear ( $n = 115$ ,  $y = 33 + 0.12x$ ,  $r = 0.62$ ,  $p < 0.001$ ).



## B Interrelations between variables

In order to avoid artificial relationships we converted all values presented in this section to a standard body surface area. All haemodynamic and volume data are therefore presented per square meter

### 1 Systemic haemodynamics

In fig. 15 the relation between mean blood pressure and cardiac index is given. At each level of blood pressure cardiac index varies widely although the range becomes narrower when pressure is higher. Furthermore cardiac index shows an inverse relationship with blood pressure ( $r = -0.16$   $p < 0.01$ )

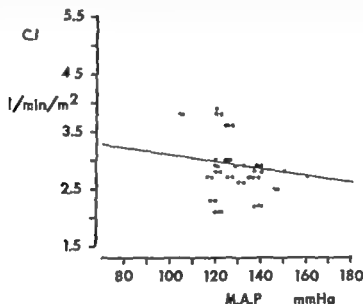


Fig. 15 Negative relationship between cardiac index and mean arterial pressure ( $n = 146$   $y = 3.7 - 0.01x$   $r = -0.16$   $p < 0.05$ )

Since peripheral resistance is derived from M.A.P. and C.O. it is strictly spoken not justified to relate this variable to the other parameters. The best approach to interrelate the two independent variables and the resultant T.P.R. appeared to be drawing them together in a three-dimensional diagram (fig. 16). This figure represents the balance between flow, calculated resistance and the resultant pressure. The most intriguing aspect of this figure is the immense variation in the interplay between flow and resistance. The higher blood pressure values tend to be dependent mainly on a high resistance.

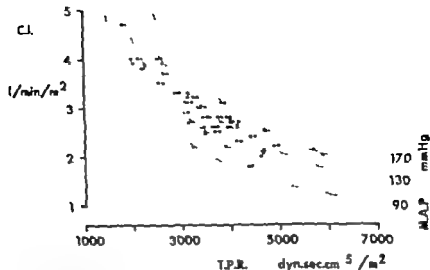


Fig. 16. Nomogram representing the balance between cardiac index, calculated total peripheral resistance and blood pressure.

## 2 Renal haemodynamics

Glomerular filtration rate in a particular way is directly related to renal plasma flow (fig. 17). When R.P.F. is lower than around 300 ml/min/m<sup>2</sup> the regression is linear ( $r = 0.6$ ,  $p < 0.001$ ) but above that point the slope of the regression line almost parallels the X axis which means that at these higher flow rates C.F.R. is practically independent of renal plasma flow. G.F.R. is inversely related to R.V.R. ( $r = -0.57$ ,  $p < 0.001$ ) as shown in fig. 18.

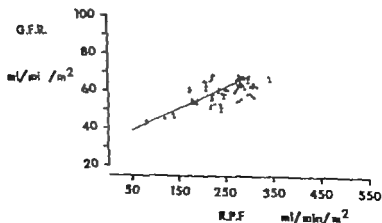


Fig. 17. Relationship between renal plasma flow and glomerular filtration rate. Up to a R.P.F. of about 300 ml/min/m<sup>2</sup> the relation is linear ( $n = 115$ ,  $y = 33 + 0.12x$ ,  $r = 0.62$ ;  $p < 0.001$ ).

## B Interrelations between variables

In order to avoid artificial relationships we converted all values presented in this section to a standard body surface area. All haemodynamic and volume data are therefore presented per square meter

### 1 Systemic haemodynamics

In fig. 15 the relation between mean blood pressure and cardiac index is given. At each level of blood pressure cardiac index varies widely although the range becomes narrower when pressure is higher. Furthermore, cardiac index shows an inverse relationship with blood pressure ( $r = -0.16$ ,  $p < 0.01$ )

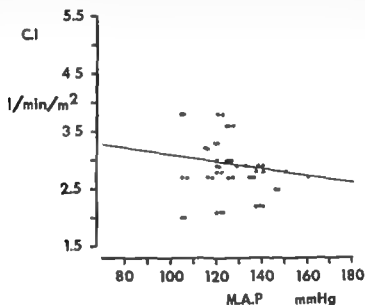


Fig. 15 Negative relationship between cardiac index and mean arterial pressure ( $n = 146$ ,  $y = 3.7 - 0.01x$ ,  $r = -0.16$ ,  $p < 0.05$ )

Since peripheral resistance is derived from M.A.P. and C.O. it is strictly spoken not justified to relate this variable to the other parameters. The best approach to interrelate the two independent variables and the resultant T.P.R. appeared to be drawing them together in a three-dimensional diagram (fig. 16). This figure represents the balance between flow, calculated resistance and the resultant pressure. The most intriguing aspect of this figure is the immense variation in the interplay between flow and resistance. The higher blood pressure values tend to be dependent mainly on a high resistance.

### 3 Systemic haemodynamics vs renal haemodynamics

There appears to be a significant inverse relationship between mean arterial pressure and renal plasma flow ( $r = -0.39$   $p < 0.001$  fig 20)

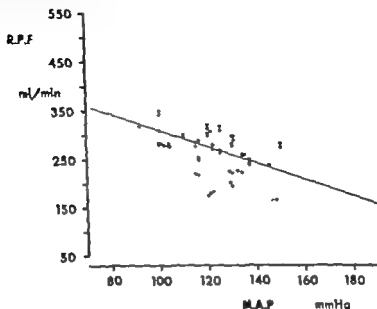


Fig 20. Relationship between mean arterial pressure and renal plasma flow ( $n = 158$   $y = 482 - 1.73x$   $r = -0.39$   $p < 0.001$ )

To a lesser degree such a relationship was also found with respect to mean blood pressure and glomerular filtration rate ( $r = -0.3$   $p < 0.01$ ). Filtration fraction was directly related to mean blood pressure ( $r = 0.45$   $p < 0.001$  fig. 21). Cardiac output and renal blood flow were found to be positively related ( $r = 0.77$   $p < 0.005$  fig. 22) whereas glomerular filtration rate and filtration fraction are not clearly proportionate to cardiac output.

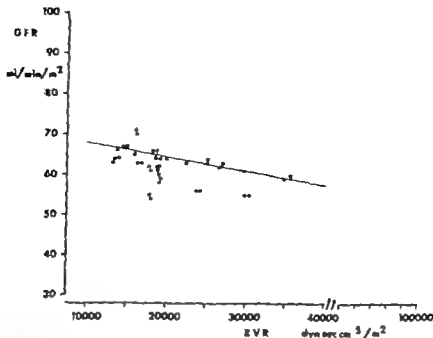


Fig 18 Relationship between renal vascular resistance and glomerular filtration rate ( $n = 139$   $y = 71 - 0.0003x$   $r = -0.57$   $p < 0.001$ )

No comparisons were made between the other parameters of renal function because they are interdependent. Nevertheless pressure flow relationships may be clarified by presenting the data on arterial pressure, renal blood flow and derived resistance values in one diagram (fig 19). As in systemic pressure flow relationships a wide scatter is observed.

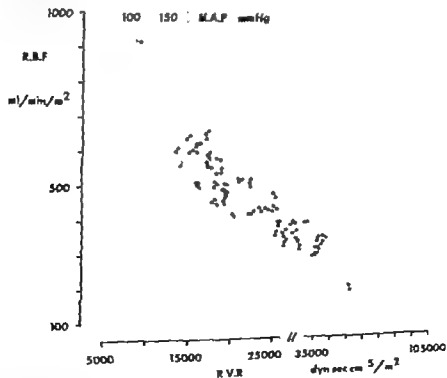


Fig 19 Nomogram representing the balance between renal blood flow, calculated renal vascular resistance and blood pressure

#### 4 Systemic haemodynamics vs body fluid volumes

Plasma volume shows a weak but insignificant tendency to increase with rising blood pressure. A similar direct relation is also observed between plasma volume and total peripheral resistance ( $r = 0.18$   $p < 0.05$  fig. 23). However, these trends are predominantly caused by a few observations. Blood volume and cardiac output were not related.

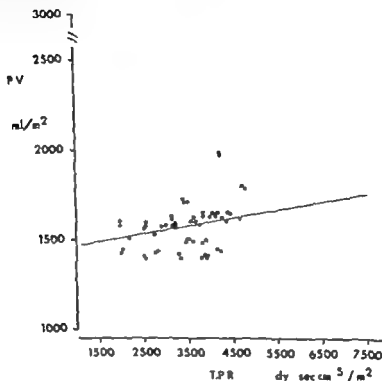


Fig. 23 Relationship between total peripheral resistance and plasma volume ( $n = 145$   $y = 1430 + 0.04x$   $r = 0.18$   $p < 0.05$ )

#### 5 Renal haemodynamics vs volumes

Plasma volume is not related to renal plasma flow or glomerular filtration rate, but it is directly related to filtration fraction ( $r = 0.25$   $p < 0.005$ ).

#### 6 Renin vs aldosterone

There appears to be no significant relationship between P.R.C. and aldosterone (fig. 4).

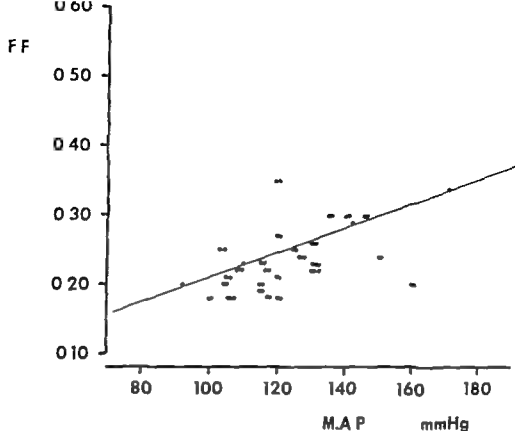


Fig. 21 Relationship between mean arterial pressure and filtration fraction ( $n = 141$   $y = 0.07 + 0.0001x$   $r = 0.45$   $p < 0.001$ )

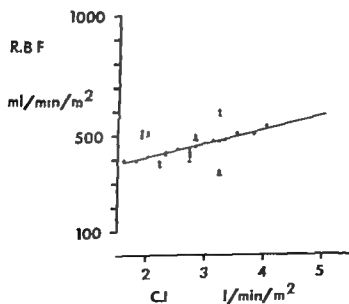


Fig. 22 Relationship between cardiac index and renal blood flow ( $n = 143$   $y = 301 + 57.3x$   $r = 0.27$   $p < 0.005$ )

## 7 Renin vs systemic haemodynamics

P.R.C. is not clearly related to mean blood pressure (fig. 25) although a tendency towards a negative relationship was detectable in patients with intact G.F.R. ( $r = -0.10$   $0.05 < p < 0.10$ ). Arbitrarily we considered a G.F.R. of less than 55 ml/min./m<sup>2</sup> as an index of depressed renal function. When patients below the age of 50 years are considered separately the relationship is no longer apparent.

P.R.C. is unrelated to C.O. and T.P.R. but here a biphasic pattern is observed. When G.F.R. is still intact renin tends to vary directly with C.O. and inversely with T.P.R. but when G.F.R. has fallen to levels below 55 ml/min./m<sup>2</sup> the relations invert none of these trends however reached statistical significance.

## 8 Renin vs renal haemodynamics

Renin is inversely related to G.F.R. ( $r = -0.28$   $p < 0.001$ ) as shown in fig. 26. On the other hand renin levels are not related to renal blood flow or filtration fraction,

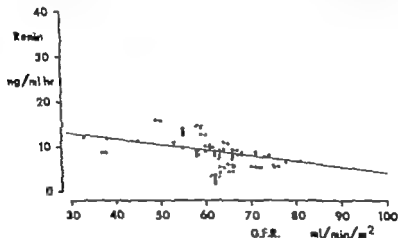


Fig. 26. Relationship between glomerular filtration rate and plasma renin concentration ( $n = 160$ ;  $y = 16.7 - 0.13x$   $r = -0.28$   $p < 0.001$ ).

even when corrected for the effect of glomerular filtration rate. In fig. 27 the relation between renin and renal vascular resistance is given. This appears to be a complex one. In the whole group renin is positively related to R.V.R. ( $r = 0.18$   $p < 0.05$ ) but a distinction can be made between patients with normal and those with subnormal G.F.R. While the former group exhibits an inverse relation between renin and R.V.R. which is bordering on statistical significance, a positive though not significant relation is found in the latter group.

## 9 Renin and aldosterone vs body fluid volumes

Renin and aldosterone are not related to plasma (or blood) volume, however in the subgroup of patients with a reduced G.F.R. renin is positively related to plasma volume ( $r = 0.37$   $p < 0.05$ ) but not to interstitial or total extracellular volume.





## Part III

### Follow-up study

Twenty-six patients, all of whom were evaluated for the cross-sectional study, could be followed up for an average period of 4.5 years. In the course of the study myocardial infarction occurred in five patients. The uncomplicated group comprised 13 men and 8 women. Mean age in this group at the start of the study was 42 years (range 25–60 years) and mean duration of follow-up was 4.6 years.

The complicated group was formed by 3 men and 7 women. At the initial investigation mean age in this group was 51 years (range 44–56 years) and significantly higher than in the uncomplicated group ( $p < 0.05$ ). Follow-up in this group on the average was 4.1 years.

In both groups the following parameters were determined during the sequential studies: blood pressure, plasma volume, renal plasma flow, renal vascular resistance and plasma renin concentration. The individual data are given in the appendix. In fig. 28 to 37 the natural course for these patients is depicted while in table 2 the means and standard errors are presented for the various parameters at the start of the study and after a variable period of follow-up.

Table 2.

Means and standard errors for the various parameters measured during follow-up at the start of the study and after the final examination

	SBAP	PA	RPF	RCR	PRC
Uncomplic. group					
start	114 ± 4	1575 ± 90	797 ± 30	21377 ± 2293	7.4 ± 0.8
final	128 ± 4	1985 ± 78	250 ± 17	25903 ± 2808	8.4 ± 0.7
	N.S.	N.S.	$p < 0.05$	N.S.	N.S.
Complic. group					
start	141 ± 5	1799 ± 86	297 ± 40	23939 ± 4641	9.1 ± 1.4
final	145 ± 16	1714 ± 136	201 ± 36	33161 ± 6615	11.1 ± 1.6
	N.S.	N.S.	$0.05 < p < 0.10$	N.S.	$p < 0.05$

Aldosterone which is not related to mean arterial pressure shows a direct relationship of borderline significance with extracellular and interstitial fluid. It is not related to the quotient  $P V / I F$

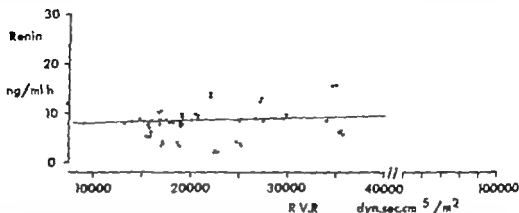


Fig 27 Relationship between renal vascular resistance and plasma renin concentration in patients with intact glomerular filtration (closed circles) and those with impaired GFR i.e. less than  $55 \text{ ml/min/m}^2$  (open circles). While the relation seems to be negative for the first group it tends to be positive for the second. For the whole group there is a significant direct relation ( $n = 139$ ,  $y = 7.6 + 0.00005x$ ,  $r = 0.18$ ,  $p < 0.05$ ).

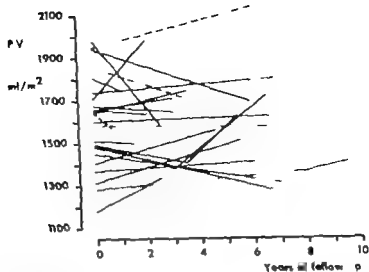


Fig. 29 Changes of plasma volume during follow-up in patients without complications (dashed lines) and in those who developed myocardial infarction (dotted lines)

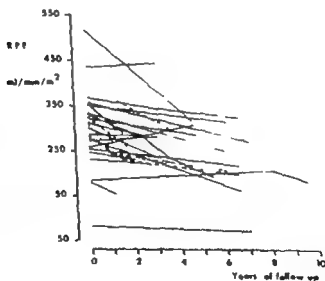


Fig. 30 Changes of renal plasma flow during follow-up in patients without complications (dashed lines) and in those who developed a myocardial infarction (dotted lines).

In the uncomplicated group no significant changes occurred in blood pressure plasma volume renal vascular resistance and plasma renin concentration although each parameter tended to increase Renal plasma flow however decreased significantly ( $p < 0.05$ )

Although mean arterial pressure plasma volume and renal vascular resistance for the complicated group at the initial study were higher than for the uncomplicated group the difference was significant only for mean arterial pressure ( $p < 0.05$ ) While there was no difference between both groups in renal plasma flow at the start renin levels were slightly but not significantly lower in the complicated group The changes in the complicated group observed during follow up showed a steeper increase in plasma renin concentration and renal vascular resistance and a more pronounced fall in renal plasma flow Due to the small number of observations and the rather wide variations in this group the changes in R V R are not significant while the reductions in R P F are only of borderline significance The increase in P R C however is statistically significant ( $p < 0.05$ )

At the end of the study mean arterial pressure plasma volume and renal vascular resistance were still somewhat higher in the complicated group although these differences were not significant Renal plasma flow was lower and plasma renin concentration was higher at this time but again the differences were not significant

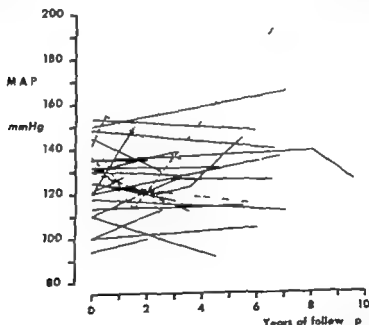


Fig 28 Changes of blood pressure during follow-up in patients without complications (dashed lines) and in those who developed myocardial infarction (dotted lines)

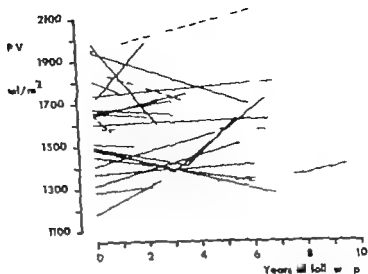


Fig 29 Changes of plasma volume during follow-up in patients without complications (dashed lines) and in those who developed myocardial infarction (dotted lines)

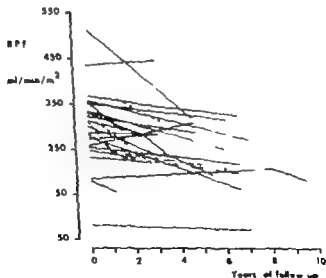


Fig 30. Changes of renal plasma flow during follow-up in patients without complications (dashed lines) and in those who developed myocardial infarction (dotted lines).

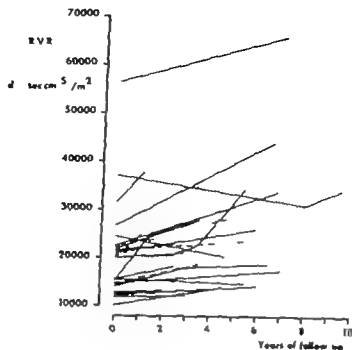


Fig 31 Changes of renal vascular resistance during follow-up in patients without complications (dashed lines) and in those who developed a myocardial infarction (dotted lines)

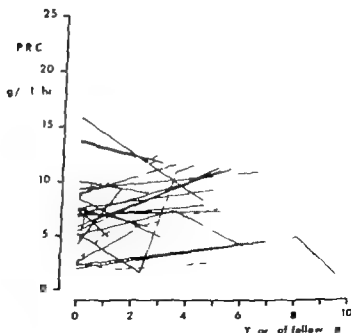


Fig. 32 Changes of plasma renin concentration during follow-up in patient without complications (dashed lines) and in those who developed myocardial infarction (dotted lines)

When alterations in the various parameters are related to each other only one significant (positive) relationship is obtained namely between changes in plasma renin concentration and in renal vascular resistance ( $r = 0.45$   $p < 0.025$ ) as shown in fig. 33. This applies to the uncomplicated group only since the complicated group is too small for this kind of analysis.

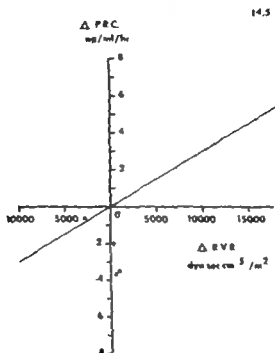


Fig. 33 Changes in plasma renin concentration versus changes in renal vascular resistance during follow-up in patients with uncomplicated (closed circles) and complicated (open circles) essential hypertension. For the uncomplicated group the relation is significant ( $n = 25$   $y = -0.03 - 0.0003$   $r = 0.45$   $p < 0.025$ ).



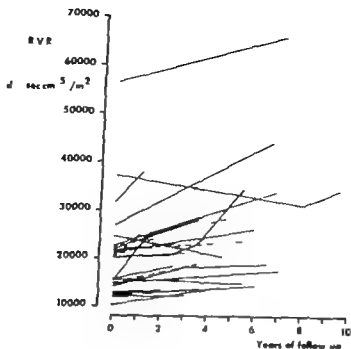


Fig 31 Changes of renal vascular resistance during follow-up in patients without complications (dashed lines) and in those who developed a myocardial infarction (dotted lines).

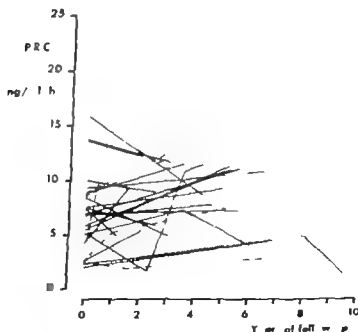


Fig 32. Changes of plasma renin concentration during follow-up in patients without complications (dashed lines) and in those who developed myocardial infarction (dotted lines)

## Part IV

### Discussion

#### Blood pressure, cardiac output and total peripheral vascular resistance

Epidemiological studies on the incidence of primary hypertension in Western countries have yielded frequencies of 15 to 70 percent (151). Obviously blood pressure is a rather erratic variable: not only are there considerable intra-individual variations during short-time observations but also age-related changes have been described. With increasing age the blood pressure tends to rise in Western culture. This upward gradient has been recognized in children as well as in adults (25, 79, 105, 110, 140, 142, 144, 706). Essential hypertension is characterized by a steeper increase with age and a more marked involvement of diastolic pressure. From our studies it is obvious that the degree of hypertension tends to be more severe in higher age groups, even though the same criterion for the diagnosis of hypertension was applied to all age groups. This feature of a progressive disorder was not obvious during actual follow-up studies. One explanation for this discrepancy may be that patients admitted to the follow-up study were not under pressure to be treated effectively because generally there was no alarming progression.

The blood pressure profile was based on systematic in-patient readings. When casual readings are taken into account the relationship with age should be less obvious since blood pressure is accepted to be more labile in the young. We have assessed variability in a sample of patients and found indeed a significant inverse relationship between variability of blood pressure and age. Even patients with hypertension starting at a higher age apparently do not disturb this general pattern. The regression is linear, there being no apparent distinction between patients with labile or more fixed hypertension.

The incidence of labile hypertension differs in several studies, but for a great deal this seems to be due to problems of definition. Therefore discussions on whether labile hypertension proceeds to sustained hypertension or not mainly depend on presumptions. Whereas variability of blood pressure appears to become less with advancing age the prevalence of this condition is not fully known. The natural history of labile hypertension has not been examined prospectively, although an excess risk of subsequent cardiovascular morbidity and mortality has been reported.



## Part IV

### Discussion

#### Blood pressure, cardiac output and total peripheral vascular resistance

Epidemiological studies on the incidence of primary hypertension in Western countries have yielded frequencies of 15 to 20 percent (151). Obviously blood pressure is a rather erratic variable: not only are there considerable intra-individual variations during short-time observations but also age-related changes have been described. With increasing age the blood pressure tends to rise in Western culture. This upward gradient has been recognized in children as well as in adults (25, 79, 105, 110, 140, 142, 144, 206). Essential hypertension is characterized by a steeper increase with age and a more marked involvement of diastolic pressure. From our studies it is obvious that the degree of hypertension tends to be more severe in higher age groups even though the same criterium for the diagnosis of hypertension was applied to all age groups. This feature of a progressive disorder was not obvious during actual follow-up studies. One explanation for this discrepancy may be that patients admitted to the follow-up study were not under pressure to be treated effectively because generally there was no alarming progression.

The blood pressure profile was based on systematic in-patient readings. When casual readings are taken into account the relationship with age should be less obvious since blood pressure is accepted to be more labile in the young. We have assessed variability in a sample of patients and found indeed a significant inverse relationship between variability of blood pressure and age. Even patients with hypertension starting at a higher age apparently do not disturb this general pattern. The regression is linear, there being no apparent distinction between patients with labile or more fixed hypertension.

The incidence of labile hypertension differs in several studies, but for a great deal this seems to be due to problems of definition. Therefore discussions on whether labile hypertension proceeds to sustained hypertension or not mainly depend on presumptions. Whereas variability of blood pressure appears to become less with advancing age the prevalence of this condition is not fully known. The natural history of labile hypertension has not been examined prospectively although an excess risk of subsequent cardiovascular morbidity and mortality has been reported.

Blood pressure results from the interaction between cardiac output and total peripheral vascular resistance. Hypertension may be the result of an increase in either one of these factors or both. In the early days it was generally thought that an increase in peripheral resistance was the main factor responsible for hypertension (14 15 26 54 73 125 178 195 196 200) although some authors stressed the importance of a high cardiac output (81 131 198). In later years this high output state has been recognized in a considerable number of patients especially in those with only mild elevation of blood pressure (6 7 9 20 32 51 53 56 59 67 84 100 101 104 111 120 136 156 159 161 186 187 192 199). Although it is held by some authors that these patients form a special subgroup the available data indicate a downward trend of cardiac output during the progression of the hypertensive disease. It is therefore possible that such patients represent an early stage of hypertension.

In most studies the high cardiac output could be attributed to an increase in heart rate (51 53 101 104 136 158 159 161 186) stroke volume being normal. In only one study an increase in stroke volume together with a normal heart rate was found (59) but in this study the patients presumably had more advanced hypertension. Others have stressed an increase both in stroke volume and in heart rate although the values for stroke volume in some of the normal subjects are lower than those reported elsewhere (6 53 104 157 159).

When excess cardiac function is mainly determined by heart rate the underlying disorder has been attributed to a combination of sympathetic overactivity and parasympathetic inhibition (102 104 117). As a corollary it may be supposed that these subjects at the time of the (invasive) measurements are more easily upset than their normotensive counterparts. In our laboratory all measurements are carried out after a sufficiently long time has passed for the patient to get accustomed to the environment. When our determinations of cardiac output in hypertensives are compared with those in normals (mainly adapted from the literature) a marked similarity is found. In fact the relation between cardiac output and age in this study does not differ much from that in normals as presented by Brandfonbrener (19). In this study equally high values for cardiac output are sometimes observed in young subjects. The decline in cardiac output with age is caused by a reduction of stroke volume which also occurs in normotensives (19).

The results of our cross sectional study confirm the positive relationship of total peripheral vascular resistance and age.

When the degree of hypertension is more severe cardiac output seems to fall in the face of an increase in total peripheral resistance (fig 15 and 16) which is in agreement with other studies (2 71 136 161).

It can be inferred from data in the literature that the natural history of hypertension is characterized by a steady increase in peripheral resistance (7 10 57 137 138 161).

However when the haemodynamic studies from various laboratories are studied more closely it appears that even at a stage when cardiac output is high peripheral resistance is increased at the same time (12).

Although renal blood flow sometimes is normal in essential hypertension (34 50 73 91 153 179) in the majority of patients renal haemodynamics are abnormal. The general pattern is found to consist of a decrease in renal blood flow and an elevation of filtration fraction and renal vascular resistance (5 15 18 21 34 44 62, 63 66 72, 73 89 90 122, 154 173). In our patients we found evidence for a considerable impact of the hypertensive process on renal haemodynamics. The blood pressure level was inversely related to renal blood flow and glomerular filtration rate and directly to filtration fraction. In the cross-sectional study we observed a negative relationship of renal blood flow with respect to age. As far as the duration of the hypertensive process is concerned the longitudinal study showed a consistent and substantial decline with time.

In view of the physiological decrease in renal blood flow due to senescence (39 97 93 114 130 153 168 169 173 197) the progressive changes in the course of hypertension should be offset against the former. In normotensives no follow-up studies are available but the relationship between renal blood flow and age is well-documented.

We have compared our results in the hypertensive patients with those reported for normal men (39 114 130 153 168 173 197) and found that the reduction of R.B.F. with age for hypertensives is generally steeper than for normal subjects. The renal fraction is normal at an early stage of hypertension but progressively diminishes with time.

With a more refined technique (Xenon-washout) we could demonstrate a significant decrease in outer cortical blood flow already in early hypertension. This phenomenon seems to be mainly responsible for the reduction of total renal blood flow (116). The following conclusions can be drawn. Firstly the results indicate that renal vascular resistance is already increased when renal blood flow is still normal. Since the renal fraction is also within normal limits, it is probable that the distribution of the cardiac output to the various organs does not differ much from that in normals at an early stage of hypertension. With increasing age secondary vascular alterations develop preferentially affecting the kidneys.

Changes in glomerular filtration become important only at a more advanced state, especially when renal blood flow has fallen to values below 300 ml/min./m<sup>2</sup>.

The findings with respect to renal haemodynamic changes support the concept of an early increase in vascular resistance as the basic hypertensive mechanism.

The nature of the increase in resistance appears to be complex. Both functional and structural components are recognizable. The functional component of the increase in renal vascular resistance can be assessed by means of saline infusions or pharmacological studies. The effects of hyperosmotic saline infusions on renal haemodynamics have been studied in our laboratory (164). Although a substantial decrease in vascular resistance could be observed the values only exceptionally decreased to the range found in normotensives. Hollenberg (94) in an attempt to discriminate between functional and structural changes infused vasodilating substances into the renal artery. His experiments revealed a quantitatively important functional vasoconstriction of the renal vessels in a number of patients with mild hypertension.

On the other hand structural changes have been thought to cause an increased

vascular resistance (3 64 170 171) From the work of Folkow (64) it has become apparent that in established hypertension the architecture of the vascular bed is altered the wall to-lumen ratio is increased presumably as a consequence of medial hypertrophy although it cannot be ruled out that the total number of arterioles is reduced as occurs in spontaneous hypertensive rats (95)

These findings can account for the haemodynamic status in advanced hypertension but do not entirely explain the situation in early (labile) hypertension

Although the resistance to blood flow in peripheral vascular beds at maximal vasodilatation was raised in borderline hypertensives thus suggesting structural changes already to be present (162) the changes in haemodynamics following physical exercise or volume expansion do not provide evidence for a decreased compliance of the vascular system (12)

Both the functional and the structural components of the increase in resistance may be the sequelae of vasoconstrictor stimuli either originating from the tissue (auto-regulation) or from increased activity on the part of pressor systems

A functional vasoconstriction has been thought to be the result of auto-regulation of tissue blood flow in response to an increased cardiac output There are several objections to this view In the first place time relations do not fit the model Whereas a substantial increase in peripheral resistance in hypertension takes many years a firm auto-regulatory control of tissue blood flow occurs much more rapidly in experimental conditions where the ability of the kidney to maintain extracellular fluid homeostasis is interfered with (8 16 29 31 42 57 58 76 78 127 129 205) In essential hypertension no direct information on such a mechanism is available Although it has been suggested that an initial rise in cardiac output is due to an increased venous return (59 190) this certainly is not due to volume expansion since plasma or blood volume in essential hypertension is normal (6 37 43 53 74 80 97 166 194) or even reduced (48 59 96 103 152 155 158 183 185 188 191) Although in the present study no comparison with normotensives was undertaken the hypertensive group per se failed to show a relationship between cardiac output or mean arterial pressure and plasma or blood volume

The most important point against autoregulation is the absence of a substantial increase in cardiac output in the younger age group

Enhanced systemic pressor activity could be based either on the renin-angiotensin system or on the adrenergic system or both Although several studies have established that values for plasma renin activity (or concentration) and aldosterone are within normal limits in most patients with hypertension rather wide ranges are found in these subjects (17 22 23 27 33 38 45 49 60 69 70 75 86 87 109 118 123 126 143 146 181) High renin levels are found in only a minority of patients with essential hypertension This already casts some doubt on the assumption that increased activity of the renin-angiotensin system plays a role in the rise of vascular resistance Moreover in about one third of patients plasma renin is abnormally low (for references see 46) In these cases renin is suppressed and unresponsive to stimuli as sodium restriction and tilting (28 35 86 87 126 175) Stronger stimuli however do raise the renin level (68 88 137 176) Low renin levels with a diminished response to stimulation have also been found in some normotensive subjects (147) The mechanism of the low renin state has not been elucidated so far Although several possibilities including mineralocorticoid excess volume expan

sion, electrolyte disturbances and reduction in sympathetic activity have been proposed to characterize low renin hypertension as a distinct nosological entity the evidence is far by conclusive.

Renin levels have been described to vary inversely with age in normotensives (136 82, 147 160) although this is not a consistent finding (148-150 153 164 167 189 204). In hypertension such a relationship has been found more often (11 148 150 160 164 167 189 204) but in some studies this could not be confirmed either (55 98 153 202).

In our cross-sectional study renin levels were also inversely related to age at least below 50 years. On the basis of these observations it can be postulated that the low renin state is a stage in the development of essential hypertension. In support of this idea is the negative relationship between renin and blood pressure observed in a number of studies (13 55 112, 115 164 182, 189 193). In other studies, however, this relationship was not found (11 74 47 134 153 202). In our study renin was also not clearly related to blood pressure although there was a weak inverse relationship between these variables in the group with intact glomerular filtration rate. This suggests some feed-back suppression of renin at higher levels of blood pressure as long as glomerular filtration is intact. Since these trends do not reach statistical significance it is probable that blood pressure per se is not the only determinant of renin secretion.

It has been reported that renin levels correlate positively with renal blood flow and inversely with filtration fraction and renal vascular resistance (145 153 163 165). These findings have been interpreted in favour of the baroreceptor theory on renin release. In this large study we failed to observe a relationship between renin and renal blood flow or filtration fraction. However a significant relation was found between renin and renal vascular resistance. This may indicate that renin secretion is governed by the combined effect of intravascular pressure and the condition of the renal vasculature. In accordance with the baroreceptor theory a rise in blood pressure will suppress renin secretion and this can happen because the pressure is transmitted along the renal vessels (133). However the drop in arterial pressure along the vascular tree in the kidney is dependent on the resistance of the intrarenal vessels. Therefore the height of the blood pressure at the level of the juxtaglomerular apparatus does not necessarily reflect the pressure as measured in a peripheral artery.

We found that a small rise in renal vascular resistance even when this is still in the normal range influences renin release. This was apparent for the cross-sectional as well as the follow-up study. Whether this is due to the accompanying reduction in glomerular filtration or to a greater fall in afferent arteriolar pressure cannot be distinguished. It is unlikely that the rise in renal vascular resistance is caused by increased renin secretion since these two parameters change in opposite directions in the early stages of hypertension.

Apparently beyond a certain age blood pressure is less easily transmitted along the renal vessels which results in more unpaired glomerular filtration and consequent stimulation of renin secretion. At this stage renin could well be involved in a further increase in renal vascular resistance as may be the case in those patients who exhibited extremely high values for their R.V.R.

In the patients below the age of 50 years the decline in renin levels could not be related to alterations in blood pressure renal function or volume status. It cannot



vascular resistance (3 64 170 171) From the work of Folkow (64) it has become apparent that in established hypertension the architecture of the vascular bed is altered the wall-to-lumen ratio is increased presumably as a consequence of medial hypertrophy although it cannot be ruled out that the total number of arterioles is reduced as occurs in spontaneous hypertensive rats (95)

These findings can account for the haemodynamic status in advanced hypertension but do not entirely explain the situation in early (labile) hypertension

Although the resistance to blood flow in peripheral vascular beds at maximal vasodilatation was raised in borderline hypertensives thus suggesting structural changes already to be present (162) the changes in haemodynamics following physical exercise or volume expansion do not provide evidence for a decreased compliance of the vascular system (12)

Both the functional and the structural components of the increase in resistance may be the sequelae of vasoconstrictor stimuli either originating from the tissue (auto-regulation) or from increased activity on the part of pressor systems

A functional vasoconstriction has been thought to be the result of auto-regulation of tissue blood flow in response to an increased cardiac output There are several objections to this view In the first place time relations do not fit the model Whereas a substantial increase in peripheral resistance in hypertension takes many years a firm auto-regulatory control of tissue blood flow occurs much more rapidly in experimental conditions where the ability of the kidney to maintain extracellular fluid homeostasis is interfered with (8 16 29 31 42 57 58 76 78 127 129 205) In essential hypertension no direct information on such a mechanism is available Although it has been suggested that an initial rise in cardiac output is due to an increased venous return (59 190) this certainly is not due to volume expansion since plasma or blood volume in essential hypertension is normal (6 37 43 53 74 80 97 166 194) or even reduced (48 59 96 103 157 155 158 183 185 188 191) Although in the present study no comparison with normotensives was undertaken the hypertensive group per se failed to show a relationship between cardiac output or mean arterial pressure and plasma or blood volume

The most important point against autoregulation is the absence of a substantial increase in cardiac output in the younger age group

Enhanced systemic pressor activity could be based either on the renin-angiotensin system or on the adrenergic system or both Although several studies have established that values for plasma renin activity (or concentration) and aldosterone are within normal limits in most patients with hypertension rather wide ranges are found in these subjects (17 22 23 27 33 38 45 49 60 69 70 75 86 87 109 118 123 126 143 146 181) High renin levels are found in only a minority of patients with essential hypertension This already casts some doubt on the assumption that increased activity of the renin-angiotensin system plays a role in the rise of vascular resistance Moreover in about one third of patients plasma renin is abnormally low (for references see 46) In these cases renin is suppressed and unresponsive to stimuli as sodium restriction and tilting (78 75 86 87 126 175) Stronger stimuli however do raise the renin level (68 88 132 176) Low renin levels with a diminished response to stimulation have also been found in some normotensive subjects (147) The mechanism of the low renin state has not been elucidated so far Although several possibilities including mineralocorticoid excess volume expan

Myocardial infarction is a well-known complication of essential hypertension and during our follow-up study this event occurred in five patients who were subsequently re-evaluated when they were in a stable condition. Although cardiac output and peripheral resistance were not consistently measured in this group the expected changes are a fall in cardiac output and a pronounced rise in vascular resistance (10).

Since myocardial infarction in this study did not influence the blood pressure levels it is likely that the maintenance of arterial pressure was largely based on the increase in total vascular resistance. This also bears some consequences for the renal circulation. Indeed the complicated group showed a greater absolute fall in renal blood flow and a steeper increase in renal vascular resistance than the uncomplicated group.

Since only five patients met with myocardial infarction we were unable to identify these differences as statistically significant.

There were only two factors which discriminated the two follow-up groups at the start of the study: age and level of blood pressure. Both were higher in the group which subsequently developed myocardial infarction. Of special interest is the observation that in this group renin levels tended to be lower while plasma volume was somewhat higher. The concept of Brunner (24) on the protective action of the low renin state although already seriously criticized by others is thus further invalidated.

Comparison of the two follow-up groups gave rise to a few more conclusions. When related to age, blood pressure in the uncomplicated group is exactly what would have been expected on the basis of the regression line from fig. 3. However, in the complicated group blood pressure is much higher than predicted by age alone. Whether this inappropriate rise has occurred suddenly or is merely the reflection of a more severe type of hypertension from the onset cannot be determined. After the myocardial event renin levels have increased significantly. This phenomenon cannot be attributed to blood pressure per se but again seems to reflect haemodynamic and pressure changes within the kidney.

be excluded therefore that the effect of hypertension is superimposed on a physiological reduction in renin secretion

When glomerular filtration rate has fallen below 55 ml/min/m<sup>2</sup> renin is directly related to plasma volume and the quotient  $P V / I F$ . This reflects the inability of blood pressure to be transmitted throughout the capillary system and explains the positive relation between plasma volume and total peripheral vascular resistance

One could argue that sodium intake could disturb the other relations by influencing renin secretion. However all our patients were in sodium balance during the studies. They received 60 mmol of sodium a day. From the original description of Laragh's group (24) where plasma renin activity is related to urinary excretion of sodium it is apparent that at an excretory level of about 60 mmol sodium a good differentiation can be made between low, normal and high renin levels. It should be borne in mind however that sodium restriction could affect plasma volume more readily in those subjects who exhibit a low renin state. Our low sodium intake regime may therefore have disturbed a negative relationship between plasma volume and P R C.

An other objection against the results could be that over the years the result of the P R C determination may have been fluctuating. We therefore have frequently tested our samples and even checked the relationships for three periods of three years. These tests did not reveal any differences in the relationships observed.

It has been stated that aldosterone levels are lower in older (normotensive) age groups (36, 61) and at higher diastolic pressures (193). Since aldosterone secretion is dependent on several factors including the renin-angiotensin system most studies on this hormone have a dynamic rather than a static character. In hypertensive subjects the role of aldosterone production has mainly been investigated in the low renin state. In these patients aldosterone secretion and excretion have been reported to be normal and sometimes less responsive than renin (28, 30, 85, 98, 113, 118, 124, 135, 148, 149, 166, 167, 201, 203). On the other hand Walker (193) demonstrated suppression of aldosterone at higher levels of blood pressure thus simulating the renin pattern. This finding argues against the concept of aldosterone excess in low renin hypertension. In our study aldosterone was not related to age, blood pressure or P R C. It only showed a borderline significant direct relation to extracellular (and interstitial) volume but not to plasma volume.

Taking all these observations together it is unlikely that the renin-angiotensin-aldosterone system is of primary importance in the elaboration of essential hypertension. As soon as substantial vascular alterations occur the system apparently becomes geared into action even before the development of malignant hypertension.

Pressor reactions could also be mediated via the alternative pathway, the adrenergic system. The activity of the adrenergic system is now being assessed by determining the level of circulating catecholamines both in the steady state and during provocative manoeuvres.

There is still much controversy at this stage and a primary role of this system in the genesis of essential hypertension remains to be proven.

## SUMMARY

In this study the results are presented of the haemodynamic and endocrinological investigation of 707 patients with essential hypertension. After establishing the relations of the various parameters with age (part IIA) interrelations between these variables are described (part IIB). The general finding is an increase in total peripheral vascular resistance early in the course of essential hypertension. In particular this rise in resistance is found in the renal vasculature.

In part III emphasis is given to the natural history of essential hypertension on the basis of a follow-up study. Again a rise in renal vascular resistance is found. As pointed out in the discussion (part IV) the cause of the abnormal resistance remains unknown. Emphasis is given to the renin-angiotensin system which plays only a minor role. Here the factors regulating long-term renin secretion are discussed in favour of the baroreceptor theory.



## SUMMARY

In this study the results are presented of the haemodynamic and endocrinological inventarisation of 707 patients with essential hypertension. After establishing the relations of the various parameters with age (part IIA) interrelations between these variables are described (part IIB). The general finding is an increase in total peripheral vascular resistance early in the course of essential hypertension. In particular this rise in resistance is found in the renal vasculature.

In part III emphasis is given to the natural history of essential hypertension on the basis of a follow-up study. Again a rise in renal vascular resistance is found. As pointed out in the discussion (part IV) the cause of the abnormal resistance remains unknown. Emphasis is given to the renin-angiotensin system which plays only a minor role. Here the factors regulating long-term renin secretion are discussed in favour of the baroreceptor theory.



## ACKNOWLEDGMENTS

The authors wish to thank Dr R. Vandongen for his critical review and constructive remarks.

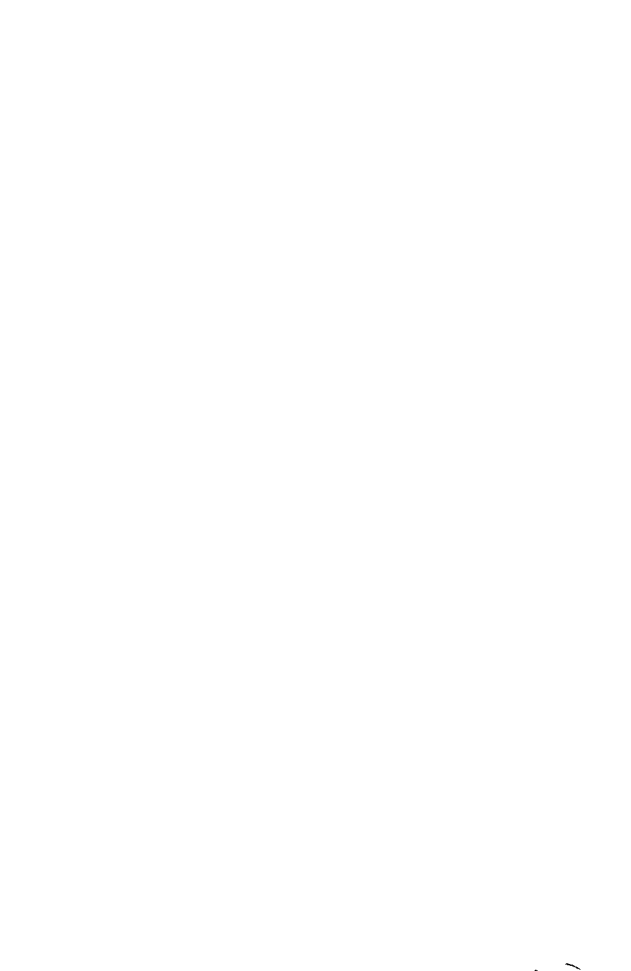
Mrs. A. van Poelvoorde, Mrs J. E. Schot and Mr R. O. Hatt were very helpful in preparing the manuscript.

We are indebted to all doctors, nurses and technical assistants, who participated in gathering the data from this study.

Studies in our department have been supported by the Organisation for Health Research, T N O The Hague, Holland (Grants GO 683-61 and GO 732-61) and by a grant from the Kidney Foundation in the Netherlands.

Publication has become possible by a Grant from the Heart Foundation in the Netherlands.





## ACKNOWLEDGMENTS

The authors wish to thank Dr H. Vandongen for his critical review and constructive remarks.

Mrs A. van Poelvoorde, Mrs. J. E. Schot and Mr R. O. Haat were very helpful in preparing the manuscript.

We are indebted to all doctors, nurses and technical assistants who participated in gathering the data from this study.

Studies in our department have been supported by the Organisation for Health Research T N O The Hague, Holland (Grants GO 683-61 and GO 732-61) and by a grant from the Kidney Foundation in the Netherlands.

Publication has become possible by a Grant from the Heart Foundation in the Netherlands.



## REFERENCES

- 1 ABE, K. IROKAWA, N. AOYAGI, H. MEMEZAWA, H. YASUJIMA, M. OTSUKA, Y., SAIKO, T. and YOSHINAGA, K. Circulating renin in essential hypertension: an evaluation of its significance in the Japanese population. *Amer Heart J* 89: 723, 1975.
- 2 AMERY, A., JULIUS, S., WHITLOCK, L. S. and CONWAY, J. Influence of hypertension on the hemodynamic response to exercise. *Circulation* 36: 231, 1967.
- 3 AMERY, A., BOSBAERT, H. and VERSTRAETE, M. Muscle blood flow in normal and hypertensive subjects. *Amer Heart J* 78: 11, 1969.
- 4 BAKER, L. E., JUDY, W. V., GEDDES, L. A., LANGLEY, F. M. and HILL, D. W. The measurement of cardiac output by means of electrical impedance. *Cardiovasc. Res. Circ. Bull.* 9: 135, 1971.
- 5 BELLO, C. T., SEVY, R. W., OKKER, E. A., PAPACOSTAS, C. A. and BUCHER, R. M. Renal hemodynamic responses to stress in normotensive and hypertensive subjects. *Circulation* 22: 573, 1960.
- 6 BELLO, C. T., SEVY, R. W. and HARAKAL, C. Varying hemodynamic patterns in essential hypertension. *Amer J Med Sci* 250: 4, 1965.
- 7 BELLO, C. T., SEVY, R. W., HARAKAL, C. and HILLYER, P. H. Relationship between clinical severity of disease and hemodynamic patterns in essential hypertension. *Amer J Med Sci* 253: 194, 1967.
- 8 BIANCHI, G., BALDOLI, E., LUCCA, R. and BARBIN, P. Pathogenesis in arterial hypertension after the constriction of the renal artery leaving the opposite kidney intact both in the anesthetized and in the conscious dog. *Clin Sci* 42: 651, 1972.
- 9 BIRKENHAGER, W. H., VAN ES, L. A., HOUWING, A., LAMERS, H. J. and MULDER, A. H. Studies on the liability of hypertension in man. *Clin Sci* 35: 445, 1968.
- 10 BIRKENHAGER, W. H., SCHALEKAMP, M. A. D. H., KRAUSS, X. H., KOLSTERS, G. and ZAAI, G. A. Concomitant hemodynamic patterns in essential hypertension. *Lancet* i: 540, 1972.
- 11 BIRKENHAGER, W. H., SCHALEKAMP, M. A. D. H., KRAUSS, X. H., KOLSTERS, G., SCHALEKAMP KUYKEN, M. P. A., KROON, B. J. M. and TEULINGS, P. A. O. Systemic and renal haemodynamics, body fluids and renal excretion in benign essential hypertension with special reference to natural history. *Europ J Clin Invest* 2: 115, 1972.
- 12 BIRKENHAGER, W. H. and SCHALEKAMP, M. A. D. H. Control mechanisms in essential hypertension. Elsevier/North-Holland Biomedical Press, Amsterdam, 1976.
- 13 BLOOMFIELD, D. K., GOULD, A. B., CANGIANO, J. L. and VERTES, V. The relationship of blood pressure to hospitalization, dietary sodium and serum renin in essential hypertension. *Angiology* 1: 75, 1970.
- 14 BRUMGART, H. L. and WEISS, S. Studies on the velocity of blood flow. IV The velocity of blood flow and relation to other aspects of the circulation in patients with arteriosclerosis and in patients with arterial hypertension. *J Clin Invest* 4: 173, 1977.
- 15 BOLOWEY, A. A., MICHIE, A. J., MICHIE, C., BREED, E. S., SCHREINER, G. E. and LAUSON, H. D. Simultaneous measurements of effective renal blood flow and cardiac output in resting normal subject and patients with essential hypertension. *J Clin Invest* 28: 10, 1949.



## REFERENCES

- 1 ABE, K. IROKAWA, N. AOYAGI, H. MEMEZAWA, H. YASUTAMA, M., OTSUKA, Y., SAJIO T. and YOSHINAGA, K. Circulating renin in essential hypertension: an evaluation of its significance in the Japanese population. *Amer Heart J* 89: 723 1975
- 2 AMERY A. JULIUS, S. WHITLOCK, L. S. and CONWAY J. Influence of hypertension on the hemodynamic response to exercise. *Circulation* 36, 231 1967
- 3 AMERY A., BOSSAERT H. and VERSTRAETE, M. Muscle blood flow in normal and hypertensive subjects. *Amer Heart J* 78 211 1969
- 4 BAKER, L. E., JUDY W. V. GEDDES, L. A. LANGLEY F. M. and HILL, D. W. The measurement of cardiac output by means of electrical impedance. *Cardiovasc. Res. Centre Bull.* 9: 135 1971
- 5 BELLO C. T. SEVY R. W. OKKER, E. A. PAPACOSTAS C. A. and BUCHER, R. M. Renal hemodynamic responses to stress in normotensive and hypertensive subjects. *Circulation* 22, 573, 1960
- 6 BELLO C. T. SEVY R. W. and HARAKAL, C. Varying hemodynamic patterns in essential hypertension. *Amer J Med Sci* 250 24 1965
- 7 BELLO C. T. SEVY R. W. HARAKAL, C. and HILLYER, P. N. Relationship between clinical severity of disease and hemodynamic patterns in essential hypertension. *Amer J Med Sci* 253 194 1967
- 8 BIANCHI G. BALDOLI E. LUCCA, R. and BARBIN P. Pathogenesis in arterial hypertension after the constriction of the renal artery turning the opposite kidney vessel both in the anesthetized and in the conscious dog. *Clin Sci* 42, 651 1972
- 9 BIRKENHAGER, W. H. VANES L. A., HOUWING, A. LAMERS, H. J. and MULDER, A. H. Studies on the liability of hypertension in man. *Clin Sci* 35 445 1968
- 10 BIRKENHAGER, W. H. SCHALEKAMP M. A. D. H. KRAUSS, X. H. KOLSTERS, G. and ZAAL, G. A. Consecutive hemodynamic patterns in essential hypertension. *Lancet* i 560, 1972
- 11 BIRKENHAGER, W. H. SCHALEKAMP M. A. D. H. KRAUSS, X. H. KOLSTERS, G., SCHALEKAMP KUYKEN M. B. A. KROON B. J. M. and TEULINGS P. A. O. Systemic and renal haemodynamics, body fluids and renin in benign essential hypertension with special reference to natural history. *Europ J Clin Invest.* 115 1972
- 12 BIRKENHAGER, W. H. and SCHALEKAMP M. A. D. H. Control mechanisms in essential hypertension. Elsevier/North Holland Biomedical Press, Amsterdam, 1976
- 13 BLOOMFIELD D. K. GOULD A. B. CANGIANO J. L. and VERTEX, V. The relationship of blood pressure to hospitalization, dietary sodium and serum renin in essential hypertension. *Angiology* 3 75 1970
- 14 BRUMGART H. L. and WEISS S. Studies on the velocity of blood flow. IV The velocity of blood flow and its relation to other aspects of the circulation in patients with atherosclerosis and in patients with arterial hypertension. *J Clin Invest* 4 373 1957
- 15 BOLOMAY A. A. MICHIE, A. J. MICHIE, C., BREED, E. S. SCHREINER, G. E. and LAUSON H. D. Simultaneous measurements of effective renal blood flow and cardiac output in resting normal subjects and patients with essential hypertension. *J Clin Invest.* 28, 10, 1949

16. BORST J Q G and BORST DE GEUS A Hypertension explained by Starling's theory of circulatory homeostasis. *Lancet* 1: 677 1963
17. BOYD G W JONES M B S and PEART W S The radioimmunoassay of angiotensin II and plasma renin activity in human hypertension. In: *Hypertension* ed. by Genest J and Koiv E. Springer Berlin 1972.
18. BRADLEY M C, CURRY J J and BRADLEY G P Renal extraction of amino-hippurate in normal subjects and in essential hypertension and chronic diffuse glomerulonephritis. *Fed. Proc.* 6: 79 1947
19. BRANDFONBRENER M, LANDOWNE M and SHOCK N W Changes in cardiac output with age. *Circulation* 11: 557 1955
20. BROD J Essential hypertension, haemodynamic observations with a bearing on its pathogenesis. *Lancet* 1: 773 1960
21. BROD J, FENCIL V, HEJL Z, JIRKA J and ULRYCH M General and regional haemodynamic pattern underlying essential hypertension. *Clin. Sci.* 3: 339 1961
22. BROWN J J, DAVIES D L, LEVER A F and ROBERTSON J I S Plasma renin concentration in human hypertension. II Renin in relation to aetiology. *Brit. Med. J.* 2: 115 1965
23. BROWN J J, DAVIES D L, LEVER A F and ROBERTSON J I S Plasma renin concentration in human hypertension. III Renin in relation to complications of hypertension. *Brit. Med. J.* 1: 505 1966.
24. BRUNNER, H R, LARACH J H, BEAR, L, NEWTON M A, GOODWIN F T, KRAKOFF L R, BARD R H and BUHLER F R. Essential hypertension, renin and aldosterone, heart attack and strokes. *New Engl. J. Med.* 286: 441 1972.
25. BUCK C. W The persistence of elevated blood pressure first observed at age five. *J. Chronic Dis.* 26: 101 1973
26. BURWELL, C S and SMITH W C The output of the heart in patients with abnormal blood pressures. *J. Clin. Invest.* 7: 1 1979
27. CATT K J, LAN E, ZIMMEL P Z, BEST J B, CAIN M D and COGHLAN J P Angiotensin II blood levels in human hypertension. *Lancet* 1: 499 1971
28. CHANNICK M J, ADLIN E. V and MARKS A D Suppressed plasma renin activity in hypertension. *Arch. Int. Med.* 133: 131 1969
29. COLEMAN T G and GUYTON A C Hypertension caused by salt loading in the dog. III Onset transients of cardiac output and other circulatory variables. *Circ. Res.* 15: 153 1969
30. COLLINS D M, WEINBERGER M H, DOWDY A. J, NOLUS G W, GONZALES G M and LUETSCHER J A Abnormally sustained aldosterone secretion during salt loading in patients with various forms of benign hypertension: relation to plasma renin. *J. Clin. Invest.* 49: 1415 1970
31. CONWAY J Hemodynamic consequences of induced changes in blood volume. *Circ. Res.* 18: 190 1966
32. CONWAY J, JULIUS S and AMERY A Effect of blood pressure on the haemodynamic response to exercise. *Hypertension* 16: 79 1968
33. COPE, C L, HARWOOD M and PEARSON J Aldosterone secretion in hypertensive diseases. *Brit. Med. J.* 1: 659 1961
34. CORCORAN A C, TAYLOR R D and PAGE, I H Circulatory responses to spinal and caudal anesthesia in hypertension: relation to the effect of sympathectomy. II Effect on renal function. *Amer. Heart J.* 36: 227 1948
35. CRANE M G, HARRIS J J and JOHNS V J Hypotensive hypertension. *Amer. J. Med.* 52: 457 1972.
36. CRANE, M G and HARRIS J J Effect of aging on renin activity and aldosterone excretion. *J. Lab. Clin. Med.* 87: 947 1976
37. CRANSTON W I and BROWN W Diurnal variation in plasma volume in normal and hypertensive subjects. *Clin. Sci.* 35: 107 1963
38. CREDITOR, M C. and LOTSCHKY U K Plasma renin activity in hypertension. *Amer. J. Med.* 43: 371 1967
39. DAVIES D F and SHOCK N W Age change in glomerular filtration rate, effective renal plasma flow and tubular excretory capacity in adult males. *J. Clin. Invest.* 29: 496 1950.
40. DEMANGE, J, PERNOD J, HAGUENEUER G and COLIN J Mesure de débit cardiaque par pléthysmographie électrique thoracique localisée. *Nouv. Presse Med.* 1: 3067 1977
41. DENNISTON J C., MAHER, J T, REEVES J T, CRUZ, J C, CYNERMAN A. and GROVER R. F Measurement of cardiac output by electrical impedance at rest and during exercise. *J. Appl. Physiol.* 40: 91 1976.

42. DISTLER, A. JUST H. J. and PHILIPP Th. Studies on the mechanism of aldosterone induced hypertension in man. *Clin. Sci. Mol. Med.* 45 743 1973
43. DISTLER, A. KEIM H. J. PHILIPP Th. PHILIPPI A. WALTER, U., WERNER, E. and WOLFF H. H. Low renin hypertension. Evidence for mineralocorticoid excess? Hypertension - Current Problems. Ed. by Distler A. and Wolff H. P. Georg Thieme, Stuttgart 1974.
44. DÖRING P. KOCH R., SANCKEN H. and SCHWAB M. Die intrarenale Hämodynamik bei essentieller Hypertonie. *Klin. Wochr.* 32: 71 1954.
45. DOYLE, A. and JERUMS G. Sodium balance, plasma renin and aldosterone in hypertension. *Circ. Res.* 76 and 27 suppl. 2: 267 1970
46. DUNN M. J. and TANNEN R. L. Low-renin hypertension. *Kidney Int.* 5 317 1974
47. DUSTAN H. P., TARAZI R. C. and FRÖHLICH E. D. Functional correlates of plasma renin activity in hypertensive patients. *Circulation* 41 555 1970
48. DUSTAN H. P. TARAZI R. C. BRAVO E. L. and DART R. A. Plasma and extracellular fluid volumes in hypertension. *Circ. Res.* 32 and 33 suppl. 1 73 1973.
49. DÜSTERDIECK, G. and McELWEE, G. M. Estimation of angiotensin II concentrations in bovine plasma by radioimmunoassay. Some applications in physiological and clinical studies. *Europ. J. Clin. Invest.* 2: 32, 1971
50. DUTZ, H. Die Bedeutung der Clearance-Methodik zur Prüfung der Nierenfunktion für die Klinik unter besonderer Berücksichtigung differenzialdiagnostischer Fragestellungen. II Nierenerkrankungen. *Z. Ges. Inn. Med.* 8 436, 1953
51. EICH R. H. PETERSON R. J. CUDDY R. P. SMULYAN H. and LYONS, R. H. The hemodynamics in labile hypertension. *Amer Heart J* 63 188 1962.
52. EICH R. J. CUDDY R. P. SMULYAN H. and LYONS, R. H. Hemodynamics in labile hypertension. *Circulation* 34 799 1966
53. ELLIS, C. H. and JULIUS, S. Role of central blood volume in hyperkinetic borderline hypertension. *Brit Heart J* 35 440 1973
54. EWIG, W. and HINSBERG, K. Über die Bestimmung des Minutenvolumens. *Klin. Wochr.* 9 647 1930.
55. FAGARD R. AMERY A. REYBROUCK, T. LUNEN P. BILLIET L. and JOOSSENS J. V. Plasma renin levels and systemic haemodynamics in essential hypertension. *Clin. Sci. Mol. Med.* 9 491 1977
56. FEJFAR, Z. and WIDIMSKI J. Juvenile hypertension. In: Proceedings of the Joint W. H. O. Czechoslovak Cardiological Society Symposium on the Pathogenesis of Essential Hypertension. Ed. by Cori J. H. Feickl, V. and Hejl Z. State Medical Publishing House, Prague 1961
57. FERRARIO C. M. PAGE, I. H. and McCUBBIN J. W. Increased cardiac output as contributory factor in experimental renal hypertension in dogs. *Circ. Res.* 7 799 1970
58. FERRARIO C. M. Contribution of cardiac output and peripheral resistance to experimental renal hypertension. *Amer. J. Physiol.* 226, 711 1974.
59. FINKIELMAN S. WORCEL, M. and AGREST A. Hemodynamic patterns in essential hypertension. *Circulation* 51 146 1965
60. FISHMAN L. M. KUCHEL, D. LIDDLE, G. W. MICHELAKIS, A. M. GORDON R. D. and CHICK W. T. Incidence of primary aldosteronism in uncomplicated "juvenile" hypertension. *J. A. M. A.* 205 497 1968.
61. FLOOD C. GHERONDACHE C. PINCUS, G. TAIT J. F. TAIT S. A. S. and MULLOUGH-BY S. The metabolism and secretion of aldosterone in elderly subjects. *J. Clin. Invest.* 46: 960, 1967
62. FOA, P. P. WOODS W. W. PEET M. M. and FOA, N. L. Effects renal blood flow, glomerular filtration rate and tubular excretory ratio in arterial hypertension. *Arch. Int. Med.* 60: 122, 1947
63. FOA, P. P. WOODS W. W. PEET M. M. and FOA, N. L. Effective renal blood flow, glomerular filtration rate and tubular excretory ratio in arterial hypertension. *Arch. Int. Med.* 71 157 1947
64. FOLKOW B. HALLBACK M. LUNDQREN Y. SIVERTSSON R. and WEISS L. Importance of adaptive changes in vascular design for establishment of primary hypertension, studied in man and in spontaneously hypertensive rat. *Hypertension* 1, 1973
65. FRASER, R. QUEST S. and YOUNG, J. A comparison of double-isotope derivative and radio-immunological estimation of plasma aldosterone concentration in man. *Clin. Sci. Mol. Med.* 45 411 1977



- 66 FRIEDMAN M BELZER A and ROSENBLUM H The renal blood flow in hypertension as determined in patients with variable, with early and with longstanding hypertension. *J.A.M.A.* 117 97 1944
- 67 FROHLICH E D TARAZI R C and DUSTAN H P Re-examination of the hemodynamics of hypertension *Amer J Med Sci* 257 9 1969
- 68 GAVRAS H RIBEIRO A II GAVRAS I and BRUNNER, H R. Reciprocal relation between renin dependency and sodium deficiency in essential hypertension *New Engl J Med.* 295 1778 1976
- 69 GENEST J BOUCHER, R. DECHAMPLAIN J VEYRAT R. CHRETIEN M BIRON P TREMBLAY G ROY P and CARTIER P Studies on the renin-angiotensin system in hypertensive patients *Canad Med Ass. J* 90:263 1964
- 70 GEORGE J GILLESPIE, L. and BARTTER F C Aldosterone secretion in hypertension. *Ann Int Med* 693 1968
- 71 GLAZER G A A study of some haemodynamic parameters in essential hypertension. *Cor Vasa* 5 165 1963
- 72 GOLDRING W CHASIS H RANGES II A and SMITH II W Effective renal blood flow in subjects with essential hypertension *J Clin Invest* 20: 637 1941
- 73 GOLDRING W and CHASIS H Hypertension and Hypertensive Disease. The Common Wealth Fund New York 1944
- 74 GROLLMAN A and SHAPIRO A D The volume of the extracellular fluid in experimental and human hypertension *J Clin. Invest* 32, 314, 1953
- 75 GUNNELLS J S GRIM C E. ROBINSON R R and WILDERMAN N M Plasma renin activity in healthy subjects and patients with hypertension. *Arch Int. Med* 119: 32, 1967
- 76 GUYTON A C and COLEMAN T G Quantitative analysis of the pathophysiology of hypertension *Circ Res.* 4 and 5 suppl 1 1 1969
- 77 GUYTON A C COLEMAN T G BOWER J D and GRANGER, H J Circulatory control in hypertension *Circ Res* 26 and 7 suppl 135 1970
- 78 GUYTON A C GRANGER, H J and COLEMAN T G Autoregulation of the total systemic circulation and its relation to control of cardiac output and arterial pressure *Circ Res.* 28 and 29 suppl 1 93 1971
- 79 HAMILTON M PICKERING G W ROBERTS J A. F and SOWRY G S C The aetiology of essential hypertension 1 The arterial pressure in the general population. *Clin. Sci* 13 11 1954
- 80 HANSEN J Blood volume and exchangeable sodium in essential hypertension *Acta Med Scand.* 184 517 1968
- 81 HAYASAKA E On the minute volume of the heart in hypertension. *Tohoku J exp Med* 9:401 1977
- 82 HAYDUK, K. KRAUSE, D K KAUFMANN W HUENGES R. SCHILLMOLLER U und UNBEHAUN V Age-dependent changes of plasma renin concentration in humans *Clin Sci. Mol Med.* 45 (suppl 1): 73s 1973
- 83 HEIDLAND A KLUTSCH K. SCHNEIDER A W and PIPPIG L Nierenhemodynamik bei kompensierter und pludekompensierter essentieller Hypertonie *Klin Wschr* 40 1003 1968
- 84 HEJL, Z. Changes in cardiac output and peripheral resistance during simple isoul influencing blood pressure. *Cardiologia* 31 375 1957
- 85 HELBER A MEURER K A WAMBACH G und KAUFMAN W Aldosterone excretion von Patienten mit essentieller Hypertonie unter Natrium-Entzug und Natrium-Belastung 1 *Hypertension-Current Problems* Ed by Dostler A and Wolff H P Georg Thieme Stuttgart 1974
- 86 HELMER O M Renin activity: blood from patient with hypertension *Canad Med A J* 90 221 1964
- 87 HELMER, O M Renin-angiotensin system and its relation to hypertension *Progr cardiovasc Dis.* 8 117 1965
- 88 HELMER O M and JUDSON W E. Metabolic studies on hypertensive patient with suppressed plasma renin activity not due to hyperaldosteronism. *Circulation* 38 965 1968
- 89 HILDEN T Diuretic clearance in essential hypertension *Acta Med Scand* Suppl 206 4 1948
- 90 HOLLENBERG N K EPSTEIN M BASCH R J COUGH N P., HICKLER, R B and MERRILL, J P Renin secretion in essential and accelerated hypertension *Amer J Med J* 851 1969
- 91 HOLLENBERG N K. In: *Progress in Nuclear Medicine* of Ed by Blauf M D Jarger Basel and University Park Press, Baltimore 1977

92. HOLLENBERG N K., ADAMS D F., MENDELL P., ABRAMS H L. and MERRILL J P Renal vascular responses to dopamine: hemodynamic and angiographic observations in normal man. *Clin Sci Mol Med* 41 733 1973
93. HOLLENBERG N K., ADAMS D F., SOLOMON H S., RASHID A., ABRAMS H L. and MERRILL J P Science and the renal vasculature in normal man. *Circ Res* 34 309 1974
94. HOLLENBERG N K., ADAMS D F., SOLOMON H., CHENITZ W R., BURGER B M., ABRAMS H L. and MERRILL J P Renal vascular tone in essential and secondary hypertension. *Medicine* 54 79 1975
95. HUTCHINS P A. and DARNELL A. E. Observation of decreased number of small arterioles in spontaneously hypertensive rats. *Circ* 44 and 35 Suppl. 1 161 1974
96. IBSEN H. and LETH A. Plasma volume and extracellular fluid volume in essential hypertension. *Acta Med Scand* 194 93 1973
97. JONES N F., CLAPHAM W F., BARRACLOUGH M A. and MILLS I H. Blood volume, total body water and aldosterone excretion in essential hypertension. *Clin. Sci.* 76 307 1964
98. JOSE, A., CROUT J R. and KAPLAN M M. Suppressed plasma renin activity in essential hypertension. *Ann Int Med* 77 9 1970
99. JUDY W. V., LANGLEY F M., MCCOWEN K. D., STINNETT D M., BAKER L E. and JOHNSON P C. Comparative evaluation of the thoracic impedance and isotope dilution methods for measuring cardiac output. *Aerospace Med* 40 51 1969
100. JULIUS S. and CONWAY J. Hemodynamic studies in patients with borderline blood pressure elevations. *Circulation* 38 382 1968
101. JULIUS S., PASCUAL A V., SANHERSTEDT R. and MITCHELL C. Relationship between cardiac output and peripheral resistance in borderline hypertension. *Circulation* 43 782 1971
102. JULIUS S., PASCUAL A. V. and LONDON R. Role of parasympathetic inhibition in the hyperkinetic type of borderline hypertension. *Circulation* 44 413 1971
103. JULIUS S., PASCUAL A. V., REILLY K. and LONDON R. Abnormalities of plasma volume in borderline hypertension. *Arch Int Med* 127 116 1971
104. JULIUS S., RANDALL O S., ESLER M B., KASHIMA T., ELLIS C N. and BENNETT J. Altered cardiac responsiveness and regulation in the normal cardiac output type of borderline hypertension. *Circ Res* 36 and 37 Suppl. 1 199 1973
105. KAHN H A., MEDALIE J H., NEUFELD H N., RISS M. and GOLDBOURT U. The incidence of hypertension and associated factors. The Israel ischemic heart disease study. *Am Heart J* 84 171 1972
106. KASS E H. and ZINNER S H. How early can the tendency toward hypertension be detected? *Malabar News Fund Q* 47 143 1969
107. KAZANIAS T M., CAXER, M P., FRANKLIN D L. and ROSS J J. Blood pressure measurement with Doppler ultrasonic flowmeter. *J Appl Physiol* 30 925 1971
108. KEINI H J., WALLACE J M., THURSTON H., CASE D B., DRAYER J L M. and LARAGH J H. Impedance cardiography for determination of stroke index. *J Appl Physiol* 41 797 1976
109. KNOXHAAR A M., SLATER J D H., JONETT T P. and PAYNE N M. Suppression of the renin-aldosterone system in mild essential hypertension. *Clin Sci Mol Med* 70 369 1976
110. KIMURA T. An epidemiological study of hypertension. *Clin Sci Mol Med* 43 (Suppl. 1) 103 s. 1973
111. KOSCHOS J M., KIRKENDALL W M., VALENCA M R. and FITZ A. E. Unilateral renal hemodynamics and characteristics of dose-response curves in patients with essential hypertension and renal disease. *Circulation* 34 29 1967
112. KLAUS M., KLUIPP F. and ZEHNER J. Suppressed plasma renin in advanced primary hypertension I. Hypertension-Current Problems, ed by Drüder A. and Wolff H. P. Georg Thieme Stuttgart 1974
113. KLOPPENDORF M. W. C., DRAYER J L M., BENRAAD M B. and BENRAAD T. J. Normal aldosterone curves supra-normal aldosterone hypertension: an alternate to normal curve low renin hypertension I. Hypertension-Current Problems, Ed by Drüder A. and Wolff H. P. Georg Thieme Stuttgart 1974
114. KLUTSCH H., HEID AND A. and OBER, A. Altersabhängigkeit der Nierenhemodynamik. *Klin Wochschr* 40 1072 1962
115. KULSTERS G., SCHALEKAMP M A D H., BIRKENHAGER W H. and LEVER A F. Renin and renal function in human essential hypertension: evidence for a renal abnormality. In: Pathophysiology and management of arterial hypertension, ed. by Berglund G., Harrison L. and Wolk L. L. Lundeberg and Sonner AB, Mölndal, 1975

- 116 KOLSTERS O De bloedsomloop door de nieren bij essentiële hypertensie Thesis, Rotterdam, 1976.
- 117 KORNER P J SHAW J UTHUR, J H WEST J J McRITCHIE, R J and RICHARDS, J G Autonomic and non-autonomic circulatory components in essential hypertension in man *Circulation* 48 107 1973
- 118 KOTCHEN T A MULROW P J MORROW L B SHUTKIN P M and MARIEB, N Renin and aldosterone in essential hypertension *Clin. Sci* 41 371 1971
- 119 KUBICEK, W G KARNEOIS J N PATTERSON R P WITSOE, D A and MATSON R. H Developments and evaluation of an impedance cardiac output system. *Aerospace Med.* 37 1208 1966
- 120 KURAMOTO K MURATA K YAZAKI Y IKEDA M and NAKAO K. Hemodynamics in the juvenile hypertension with special reference to the response to propranolol. *Jap. Circ. J* 32 981 1968
- 121 LABABIDI A EHMKE D A DURNIN R E LEAVERTON P E and LAYER, R M Evaluation of impedance cardiac output in children. *Pediatrics* 47 870 1971
- 122 LADEFOGED J Renal circulation in hypertension *Munksgaard Copenhagen* 1968.
- 123 LARAGH J H ULICK S JANUSZEWICZ, V DEMING Q B KELLY W G and LIEBERMAN S Aldosterone secretion in primary and malignant hypertension. *J. Clin. Invest.* 39 1091 1960
- 124 LARAGH J H SEALEY J and BRUNNER H R. The control of aldosterone secretion in normal and hypertensive man: abnormal renin-aldosterone pattern in low-renin hypertension. *Amer J Med* 53 649 1972
- 125 LAUTER S and BAUMANN H. Über den Kreislauf bei Hochdruck, Arteriosklerose und Apoplexie. *Z. Klin Med* 109 415 1928
- 126 LEDINGHAM J G G BULL, M G and LARAGH J H The meaning of aldosteronism in hypertensive disease. *Circ. Res.* 20 and 1 suppl. 177 1967
- 127 LEDINGHAM J M and COHEN R D The role of the heart in the pathogenesis of renal hypertension. *Lancet* ... 979 1963
- 128 LEDINGHAM J M and COHEN R D Changes in extracellular fluid volume and cardiac output during the development of experimental renal hypertension. *Canad. Med. Ass. J* 90 792 1964
- 129 LEDINGHAM J M and PELLING D Cardiac output and peripheral resistance in experimental renal hypertension in rats. *Circ. Res.* 20 and 1 suppl. 187 1967
- 130 LEE, T D LINDEMAN R D YIENGST M J and SHOCK N W Influence of age on the cardiovascular and renal response to tilting. *J Appl Physiol* 1 55 1966
- 131 LILJESTRAND G and STENSTROM M Clinical studies on the work of the heart during rest. III Blood flow in cases of increased arterial blood pressure with observations on the influence of pregnancy on the blood flow. *Acta Med Scand* 63 142 1925
- 132 LOWDER S C and LIDDLE, G W Prolonged alteration of renin responsiveness after spronolactone therapy. *New Engl J Med* 291 1 43 1974
- 133 LOWENSTEIN J BERANBAUM E R CHASIS, H and BALDWIN D S Intrarenal pressure and exaggerated natriuresis in essential hypertension. *Clin Sci* 38 359 1970.
- 134 LUCAS C P HOLZWARHT G J OCOBOCK R W SOZEN T STERN M P WOOD P D S. HASKELL, W L. and FARQUHAR J W Disturbed relationship of plasma renin to blood-pressure in hypertension. *Lancet* 1377 1974
- 135 LUETSCHER J A BECKERHOFF R DOWDY A J and WILKINSON M Incomplete suppression of aldosterone secretion and plasma concentration in hypertensive patient on high sodium intake. In: Hypertension ed by Genest J and Kohn E. Springer Berlin 1972
- 136 LUND-JOHANSEN P Hemodynamics in early essential hypertension. *Acta Med Scand* 181 Suppl 482, 1967
- 137 LUND-JOHANSEN P Hemodynamic alteration in essential hypertension. In: Hypertension Mechanisms and Management. Proceedings of the 76th Hahnestamm Symposium. Ed by Onizuki G, Kim, K. E. and Moyer J H Grune and Stratton, New York - London 1973
- 138 LUND-JOHANSEN P Hemodynamic trends in untreated essential hypertension. Preliminary report on a 10 year followup study. *Acta Med Scand Suppl* 68... 1976.
- 139 MALVANO R GANDOLFI C GIANNESI D GIANOTTI P and GROSSO P Radioimmunoassay of aldosterone in crude plasma extracts. *J Nucl Biol Med* 70 17 1976
- 140 MASTER A M DUBLIN L. I and MARSH H H The normal blood pressure range and its clinical implications. *J A M A* 143 1464 1940

- 141 McINTOSH H D BURNUM J P HICKAM J B and WARREN J V Circulatory changes produced by the Valsalva maneuver in normal subjects, patients with aortic stenosis and autonomic nervous system alterations. *Circulation* 9: 511 1954
- 142 McLAIN L G Hypertension in childhood: review *Amer Heart J* 92: 634 1976.
- 143 MEYER, P., ALEXANDRE, J M DEVAUX, C. LEROUX-ROBERT, C. et MILLIEZ, P. Détermination de l'activité rénine plasmatique chez 261 hypertendus. *Presse Méd.* 40: 2025 1966.
- 144 MIALL, W. E. and CHINN S Blood pressure and ageing: results of fifteen to seventeen year follow-up study in South Wales. *Clin. Sci. Mol. Med.* 45 (Suppl 1): 23 s, 1973
- 145 MOLZAHN M DISSMANN T HALIM S LOHMANN F W and OELKERS W Orthostatic changes of haemodynamics, renal function, plasma catecholamines and plasma renin concentration in normal and hypertensive man. *Clin. Sci.* 42, 209 1972.
- 146 NIELSEN I and JACOBSEN J Plasma renin activity and aldosterone secretion rate in hypertension. *Acta Med. Scand.* 187: 401 1970.
- 147 NOTH R. H. LASSMAN M N TAN S Y FERNANDEZ-CRUZ, A and MULROW P J Low plasma renin activity (PRA) in normotensive subjects (abstract) *Clin Res.* 23: 199 1975
- 148 PADFIELD P L, BEEVERS D G, BROWN J J DAVIES D L LEVER, A F ROBERTSON J I S SCHALEKAMP M A D H and TREE, M I low-renin hypertension: stage in the development of essential hypertension or diagnostic entity. *Lancet* i: 548 1975
- 149 PADFIELD P L, BEEVERS D G BROWN J J DAVIES, D L, FRASER, R LEVER, A F and ROBERTSON J I S. with SCHALEKAMP M A D H KOLSTERS, G and BIRKENHÄGER, W H Low-renin hypertension: diagnostic entity attributable to mineralocorticoid excess. In: *Hypertension: its nature and treatment* ed by Berley D M Birchwood G, F B Fryer J H and Taylor S H Ciba Laboratories, Horsham, 1975
- 150 PADFIELD P L, NELSON C S BEEVERS D G HAWTHORNE, V M GREAVES D A DUNCAN S BLYTH M and YOUNG J Hypertension and the renin-angiotensin system in an unselected population. I. Hypertension: its nature and treatment, ed. by Berley D M Birchwood, G. F B Fryer J H and Taylor S H Ciba Laboratories, Horsham 1975
- 151 PAGE, L. B. Epidemiologic evidence on the etiology of human hypertension and its possible prevention *Amer Heart J* 91: 177 1976
- 152 PARVING, H. M. ROSSING M and JENSEN H A E. Increased metabolic turnover rate and intracapillary escape rate of albumin in essential hypertension. *Circ. Res.* 33: 544 1974
- 153 PEDERSEN H B and KORNERUP H J Renal haemodynamics and plasma renin in patients with essential hypertension. *Clin Sci Mol Med* 40: 409 1976
- 154 PFEIFFER, J B WOLFF H O and WINTER, O S Studies in renal circulation during periods of 'stress' and accompanying emotional reactions in subjects with and without essential hypertension: observations on the role of arterial activity in regulation of renal blood flow. *J. Clin. Invest.* 79: 1227 1960
- 155 ROCHLIN D B SHOHLT and BLAKEMORE, W S Blood volume changes associated with essential hypertension. *Surg Gynecol Obstet* 111: 569 1960
- 156 ROYE G Q CASTILLO C A MAXWELL, G M and CRUMTON C W A haemodynamic study of hypertension including observations on coronary blood flow. *Ann Int Med.* 54: 405 1961
- 157 SAFAR M FENDLER J P WEIL, B IDATTE, J M BEUYE-MERY P et MILLIEZ, P Étude hémodynamique de l'hypertension artérielle labile. *Presse Méd.* 78: 111 1970
- 158 SAFAR, M E WEISS Y A LEVENSON, J A LONDON G M and MILLIEZ, P L Hemodynamic study of 85 borderline hypertensive patients. *Amer J Card.* 31: 315 1973
- 159 SAFAR M F LONDON G M WEISS, Y A. and MILLIEZ, P L Vascular reactivity to norepinephrine and hemodynamic parameters in borderline hypertension. *Amer Heart J* 89: 490 1975
- 160 SAMBHI H P CRANE, M G and GENEST J Essential hypertension: new concepts about mechanisms. *Ann Int Med* 79: 411 1973
- 161 SANNERSTEDT R Hemodynamic response to exercise in patients with arterial hypertension. *Acta Med Scand* 180 (Suppl 458): 1 1966
- 162 SANNERSTEDT R SIVERTSSON R and LUNDGREN Y Hemodynamic studies in young men with mild blood pressure elevation. *Acta Med Scand.* (Suppl 802): 61 1976
- 163 SCHALEKAMP M A D H SCHALEKAMP KUYKEN M P A. and BIRKENHÄGER, W H Abnormal renal haemodynamics and renal suppression in hypertensive patients. *Clin. Sci.* 39: 101 1970

- 116 KOLSTERS G De bloedsomloop door de nieren bij essentiële hypertensie. Thesis, Rotterdam 1976.
- 117 KORNER P I SHAW J UTHUR J B WEST J J McRITCHIE, R J and RICHARDS J G Autonomic and non-autonomic circulatory components in essential hypertension in man. *Circulation* 48: 107 1973
- 118 KOTCHEN T A MULROW P J MORROW L II SHUTKIN P M and MARIEB N Renin and aldosterone in essential hypertension. *Clin Sci* 41: 31 1971
- 119 KUBICEK W G KARNEGIS J N PATTERSON R P WITSOE, D A. and MATSON R. H. Developments and evaluation of an impedance cardiac output system. *Aerospace Med* 37: 1708 1966
- 120 KURAMOTO K, MURATA K YAZAKI Y IKEDA M and NAKAO K. Hemodynamics in the juvenile hypertension with special reference to the response to propranolol. *Jap Circ J* 32: 981 1968
- 121 LABABIDI A EHMKE, D A DURNIN R E. LEAVERTON P E. and LAVER R. M. Evaluation of impedance cardiac output in children. *Pediatrics* 47: 870 1971
- 122 LADEFOGED J Renal circulation in hypertension. Munksgaard, Copenhagen 1968
- 123 LARAGH J H ULICK S JANUSZEWICZ, V DEMING Q B KELLY W G and LIEBERMAN S Aldosterone secretion in primary and malignant hypertension. *J Clin Invest* 39: 1091 1960
- 124 LARAGH J H SEALEY J and BRUNNER H R. The control of aldosterone secretion in normal and hypertensive man: abnormal renin-aldosterone patterns in low-renin hypertension. *Amer J Med* 43: 649 1972
- 125 LAUTER S and BAUMANN H. Über den Kreislauf bei Hochdruck. *Arteriosklerose und Apoplexie. Z. Klin Med* 109: 415 1928
- 126 LEDINGHAM J G G BULL, M G and LARAGH J H. The meaning of aldosteronism in hypertensive disease. *Circ Res* 20 and 1 suppl.: 177 1967
- 127 LEDINGHAM J M and COHEN R. D. The role of the heart in the pathogenesis of renal hypertension. *Lancet*: 979 1961
- 128 LEDINGHAM J M and COHEN R. D. Changes in extracellular fluid volume and cardiac output during the development of experimental renal hypertension. *Canad Med Ass. J* 90: 79 1964
- 129 LEDINGHAM J M and PELLING D. Cardiac output and peripheral resistance in experimental renal hypertension in rats. *Circ Res* 20 and 1 suppl.: 187 1967
- 130 LEE T D LINDEMAN R. D. YIENGST M J and SHOCK N. W. Influence of age on the cardiovascular and renal response to tilting. *J Appl Physiol* 1: 53 1966.
- 131 LILJESTRAND G and STENSTROM M. Clinical studies on the work of the heart during rest. III Blood flow in cases of increased arterial blood pressure with observations on the influence of pregnancy on the blood flow. *Acta Med Scand* 63: 142, 1923
- 132 LOWDER, S C and LIDDLE G W. Prolonged alteration of renin responsiveness after spironolactone therapy. *New Engl J Med* 291: 143 1974
- 133 LOWENSTEIN J BERANBAUM E. R. CHASIS H and BALDWIN D. S. Intrarenal pressure and exaggerated natriuresis in essential hypertension. *Clin Sci* 38: 359 1970.
- 134 LUCAS C P HOLZWARTH G J OCOBOCK R W SOZEN T STERN M P WOOD P D S HASKELL W L and FARQUHAR J W. Disturbed relationship of plasma renin to blood-pressure in hypertension. *Lancet*: 1337 1974
- 135 LUETSCHER J A BECKERHOFF R DOWDY A J and WILKINSON R. Incomplete suppression of aldosterone secretion and plasma concentration in hypertensive patient on high sodium intake. In: *Hypertension* ed by Genest J and Korw E. Springer Berlin 1975
- 136 LUND-JOHANSEN P. Hemodynamics in early essential hypertension. *Acta Med Scand* 181 Suppl. 482, 1967
- 137 LUND-JOHANSEN P. Hemodynamic alterations in essential hypertension. I. Hypertension Mechanisms and Management. *Proceedings of the 76th Hahnemann Symposium* Ed by Orsz G. Klin, K. E. and Moyer J. H. Grune and Stratton. New York - London, 1973
- 138 LUND-JOHANSEN P. Hemodynamic trend in untreated essential hypertension. Preliminary report on a 10 year follow-up study. *Acta Med Scand Suppl* 60, 1976
- 139 MALVANO R. GANDOLFI C GIANNESI D GIANOTTI P and GROSSO P. Radioimmunoassay of aldosterone in crude plasma extracts. *J Nucl Biol Med* 20: 37 1976
- 140 MASTER, A M DUBLIN L. I and MARKS H. H. The normal blood pressure range and its clinical implications. *J A M A* 143: 1464 1950

- 189 TUCK, M. L. WILLIAMS G. H. CAIN J. P., SULLIVAN J. M. and DLUHY R. G. Relation of age, diastolic blood-pressure and known duration of hypertension to prevalence of low-renin essential hypertension. *Amer J Cardiol* 3: 637 1973.
- 190 ULRYCH M. FROHLICH E. D. DUSTAN H. P. and PAGE, I. H. Cardiac output and distribution of blood volume in central and peripheral circulations in hypertensive and normotensive men. *Brit. Heart J* 31: 470 1969.
- 191 ULRYCH M. Plasma volume decrease and elevated Evans blue disappearance rate in essential hypertension. *Clin. Sci. Mol. Med.* 45: 173 1973.
192. VARNAUSKAS E. Studies in hypertensive cardiovascular disease with special reference to cardiac function. *Scand J Clin Lab Invest.* 7 Suppl. 17: 1 1955.
- 193 WALKER, W. G. HORVATH J. S. MOORE, M. A., WHELTON P. and RUSSELL, R. P. Relation between plasma renin activity, angiotensin and aldosterone and blood pressure in mild untreated hypertension. *Circ. Res.* 38: 470 1976.
- 194 WALSER, M. DUFFY B. J. and RIFFIN H. W. Body fluids in hypertension and mild heart failure. *J. A.M.A.* 160: 858, 1946.
- 195 WEISS, S. and ELLIS L. B. Quantitative aspects and dynamics of the circulatory mechanisms in arterial hypertension. *Amer Heart J* 9: 448, 1930.
- 196 WERKO L and LAGERLOF H. Studies on the circulation in man: cardiac output and blood pressure in the right atricle, right ventricle and pulmonary artery in patients with hypertensive cardiovascular disease. *Acta Med. Scand.* 131: 477 1949.
- 197 WESSON L. G. Physiology of the human kidney. Grune and Stratton Inc. New York, London, 1969.
- 198 WEZLER K. and BOGER, A. Die Dynamik des arteriellen Systems. Der arterielle Blutdruck und seine Komponenten. *Ergeb. Physiol* 41: 792, 1939.
- 199 WIDIMSKI J. FEJFARVAD H. M. and FEJFAR, Z. Der jugendliche Hochdruck. *Arch. Kreis.-Forch* 38: 100 1948.
- 200 WIGGERS C. J. The dynamics of hypertension. *Amer Heart J* 16: 15 1938.
- 201 WILLIAMS G. H. LAULER D. P. and DLUHY R. G. Aldosterone response to volume manipulation: normal man, hypertension I. Hypertension. Ed. by Clement, J. and Kore, E. Springer, Berlin, 1972.
202. WISENBAUGH P. E. GARST J. B. HULL, C. L. FREIDMAN R. J. MATTHEWS, D. N. and HADADY M. Renin, aldosterone, volume and hypertension. *Amer J Med* 52: 175 1972.
- 203 WOODS J. W. LIDOLE G. W. STANT E. G. MICHELAKIS A. M. and BRILL, A. B. Effect of an adrenal inhibitor in hypertensive patients with suppressed renin. *Arch. Int. Med.* 139: 1969.
- 204 WOODS J. W., PITTMAN A. W. PULLIAM C. C. WERK E. E. WARDL, W. and ALLEN C. A. Renin profiling in hypertension and its use in treatment with propranolol and chlorthalidone. *New Eng J Med* 294: 1117 1976.
- 205 ZAAL, G. A. STRANG K. D. NOLSTERS G. SCHALEKAMP W. A. H. and BIRKENHAGER, W. H. Haemodynamic changes during reversible hypertension due to liponized angiotensin. *Neth J Med* 16: 169 1973.
- 206 ZINNER S. H. LEVY P. S. and KASS E. A. Familial aggregation of blood pressure in siblings. *N. Engl J Med* 294: 401 1976.

- 164 SCHALEKAMP M A D H KRAUSS X H SCHALEKAMP KUYKEN M P A A KOLSTERS G and BIRKENHAGER, W H Studies on the mechanism of hypernatremia in essential hypertension in relation to measurements of plasma renin concentration, body fluid compartments and renal function. *Clin Sci* 41: 19 1971
- 165 SCHALEKAMP M A D H SCHALEKAMP KUYKEN M P A., DE MOOR FRUYTIER, M MEININGER Th VAANDRAAGER KRANENBURG D J and BIRKENHAGER, W H Interrelationships between blood pressure, renin, renin substrate and blood volume in terminal renal failure. *Clin Sci Mol Med* 45: 417 1973
- 166 SCHALEKAMP M A D H LEBEL, M BEEVERS D G FRASER R KOLSTERS G and BIRKENHAGER, W H Body-fluid volumes in low-renin hypertension. *Lancet* ... 310, 1974
- 167 SCHALEKAMP M A D H BIRKENHAGER, W H KOLSTERS G and LEVER, A. F Pathogenetic aspects of low-renin hypertension. In: *Hypertension - Current Problems*, ed by Distler A and Wolff A P Georg Thieme Stuttgart 1974
- 168 SHOCK, N W Inulin, diodrast and urea clearance studies on aged human subjects. *Fed. Proc.* 4: 63 1945
- 169 SHOCK, N W Kidney function tests in aged males. *Geriatrics* 1: 3, 1946.
- 170 SIVERTSSON H and OLANDER R. Aspects of the nature of the increased vascular resistance and increased reactivity to noradrenaline in hypertensive subjects. *Life Sci* 7: 1291 1968
- 171 SIVERTSSON R. The hemodynamic importance of structural vascular changes in essential hypertension. *Acta Physiol. Scand.* 79 Suppl 343: 28 1970
- 172 SKINNER E L. Improved assay methods for renin concentration and activity in human plasma. *Circ Res.* 20: 391 1967
- 173 SMITH H W *The Kidney: Structure and function in health and disease* Oxford Medical Publication Oxford University Press New York 1951
- 174 SMITH J J BUSH J E WIEDMEIER V T and TRISTANI F E. Application of impedance cardiography to study of postural stress. *J Appl Physiol* 29: 133 1970
- 175 SPARK, R. F and MELBY J C. Hypertension and low plasma renin activity: presumptive evidence for mineralocorticoid excess. *Ann Int Med* 75: 831 1971
- 176 SPARK, R. F O'HARA C M and REGAN R M. Low-renin hypertension: Restoration of normotension and renin responsiveness. *Arch Int Med* 133: 705 1974
- 177 SPARLING C M Registratie en kwantitatieve interpretatie van klierstof-erdrukningscurves verkregen door reflectie-meting in rood of infrarood licht. Thesis Groningen, Van Gorkum A van 1961
- 178 STARR, I DONALD, J S MARGOLIES A. SHAW R. COLLINS L H and GAMBLE C J. Studies of heart and circulation in disease: estimation of basal cardiac output, metabolic volume, heart size and blood pressure in 35 subjects. *J Clin Invest* 13: 561 1934
- 179 STEINITZ, K. Zur Frage der Nierendurchblutung bei normalen Hypertonikern und Nierenkrankheiten. *Acta Med Scand* 109: 95 1941
- 180 STOCKIGT J R COLLINS R D and BIGLIERI E. G. Determination of plasma renin concentration by angiotensin I immuno-assay. *Circ Res.* of 78 and 79 Suppl 175 1971
- 181 STREETEN D H P SCHLETTER F E CLIFT G V STEVENSON C T and DALAKOS T G. Studies on the renin-angiotensin-aldosterone system in patients with hypertension and in normal subjects. *Amer J Med* 46: 844 1969
- 182 STROOBANDT R FAGARD R. ROUSSEL DERUYCK R and AMERY A. Plasma renin concentration in essential hypertension and incidence of stroke and heart attack. In: *Hypertension: Arteriosa*, ed by Zanchetti A. Boehringer Ingelheim, s.p.a. Firenze 1973
- 183 TARAZI R C FROHLICH E. D and DUSTAN H P. Plasma volume in men with hypertension. *New Engl J Med* 278: 76, 1968
- 184 TARAZI R C DUSTAN H P and FROHLICH E. D. Relation of plasma to interstitial fluid volume in essential hypertension. *Circulation* 40: 357 1969
- 185 TARAZI R. C DUSTAN H P FROHLICH E. D GIFFORD W and HOFFMAN G C. Plasma volume and chronic hypertension. *Arch Int Med* 125: 815 1970
- 186 TARAZI R. C IBRAHIM M M DUSTAN H P and FERRARIO C M. C redue factors in hypertension. *Circ. Res.* 34 and 35 Suppl 1: 13 1974
- 187 TAYLOR S H DONALD K. W and BISHOP J B. Circulatory studies in hypertensive patients at rest and during exercise. *Clin Sci* 16: 351 1957
- 188 TIBBLIN G BERGENTZ, S E BJURE, J and WILHELMSEN L. Hematocrit, plasma protein, plasma volume and viscosity in early hypertensive disease. *Amer Heart J* 72: 165 1966

## APPENDIX





Table A 1

Individual (raw) data for all 207 patients included in the cross-sectional study

Nr	Sex	Height	Weight	B S A	Age	M A P	Var	Dye	C O	Imp	T P R	P V	
1	M				54	140		6,53			1715		
2	M	173	61,2	173	56	110	26			6,8	1294	2713	1
3	F	168	70	180	50	122	11	3,76			2596	2450	1
4	M	166	81	189	66	137				5,9	1858	2839	1
5	M	173	69	182	39	140				5,1	2196	2619	1
6	M	179	76	194	37	100	33	5 8			1560	2660	1
7	M	178	72,5	190	43	125				4,4	2273	2680	1
8	M	173	74	187	34	105		3 8		4 2	2222	2702	1
9	F	161	65	168	70	-							
10	F	173	62	174	35		32					2678	1
11	F	175	79	194	38	116	41	4 7			1870	2895	1
12	F	175	76	191	42							2636	1
13	F	175	75	190	45	127				5,1	1992	3257	
14	M	176	83,5	199	57	87		4,3		4,0	1619	2154	1
15	M	184	68,8	190	17	105		8,2			1024	2914	1
16	M	172	74,4	185	53	163		5,12			2552		
17	M	170	70	181	55							3196	1
18	M	169	74	184	56	147				4 6	2557	3106	1
19	M	177	68 8	185	45	140						2748	1
20	M	172	84	197	55	131	41	7,8			1310	3150	1
21	F	164	68	174	61	145		4,1			2829	3000	1
22	M	183	87	210	28	122				7 8	1251	3634	1
23	F	160	53	154	56	115	32	3,08			2987	2360	1
24	M	170	64	174	39	113	50	8 1			1150	2745	1
25	M	181	85 9	206	44	100				5,1	1569	3732	1
26	M	181	84,9	206	45	100	22			3 6	2222	3430	1
27	M	165	75 1	182	52	137				4 1	2673	2585	1
28	M	170	71 2	183	31	115	14			4 6	2000	2571	1
29	M	178	74	192	41	120		3 96			2424	2274	1
30	M	176	83 5	200	30	137				5 5	1993	3100	
31	M	175,5	82 2	198	36	105	42			5 3	1585	3196	
32	F	171	68 1	179	37	110				6 2	1419	2664	1

P V	C V	Cyano O P F	Insulin	R P R	R B R	R V R	P	P R C	P Aldo
3024			103	303	561	15 686	0 34	12 4	10 9
3952		111		407	656	14 878	0 27	2 4	
3357		102	111	453	871	12 583	0 25	14 1	18 8
4762	11 0	76	79	267	485	23 093	0 30	21 3	26 7
4508	15 5	123		677	1167	6 855	0 18	8 0	
5154			120	586	1126	8 880	0 20	8 8	6 4
5004	9 4	120	127	420	778	10 797	0 30	8 8	10 9
		120	110	367	655		0 30	10 5	
4463									
4991	13,0	148		720	1241	7 478	0 21	5 6	
4321	10 2	120		643	1057		0 19	5 4	
5428			147	608	1030	9 864	0 24	4 0	13 7
3916				419	776	8 969		8 3	15 6
5024	10 7	127	121	684	1140	7 368	0 18	15 9	
	12 8							26 6	3 1
5922		114	96	341	631		0 28	16 1	6 7
5860			91	329	621	18 937	0 28	15 9	9 4
4738	7 6	116	113	537	1013	11 056	0 21	9 8	
5250	15 2	130		568	979	10 705	0 23	4 4	
4688	12 7	127		513	916	12 664	0 25	2 8	
6730				707	1309	7 456		7 5	21 7
3471	8,8	96		484	793	11 602	0 20	2 2	
4733				225	409	22 103		16	
6547			146	577	1030	7 767	0 25	8 5	6 3
6236			129	581	1056	7 576	0 22	7 3	11 8
4700				435	806	13 598		4 4	24 3
4944	9 6		99	505	935	9 840	0 20	13 0	6 3
3610			105					9 6	
5849				693	1308	8 379		10 3	8 9
5510			126	483	833	10 084	0 26	7 7	7 4
4298				524	832	10 577		3 4	

Nr	Sex	Height	Weight	B S A	Age	M A P	Var	Dye	C O	Imp	F P R	V	
33	F	160	59,8	162	19	123				5,4	1822	2392	
34	F	159	57,6	158	54	123				3,9	2523	2162	
35	F	162	63,6	168	62	175		3,66			3825		
36	F	164	70	176	44		21					2223	
37	F	163	72	176	45	116		3,7			2660	2274	
38	F	163	68	174	49	146		4,33			2697		
39	F	164	72,9	179	53	127				7,2	1411	2517	
40	M	162	65	169	50	132		4,34			2439	2939	
41	F	165	65	171	61	134		8,8		5,7	1218	2336	
42	M	180	68,2	186	36							3100	
43	M	179,5	70	188	38	103	44			3,49	2361	3095	
44	M	180	83	202	37	108						3621	
45	F	154	48,8	144	39	139				2,99	3719	2341	
46	F	163	53	156	34							2138	
47	M	185	87,6	212	41	178		5,88			2422		
48	M	182	74,4	195	60	135	26			5,1	2118	3613	
49	M	194	95	226	29	111		7,37			1210	2994	
50	F	163	64,9	170	27							2327	
51	M	182	76,3	197	27	127		7,2			1411	3288	
52	M	182	79,4	200	29	114				5,28	1720	3431	
53	F	158	65,2	166	68	183						2439	
54	F	158	64	165	69	142				2,82	4028	2730	
55	M	182	81	202	41	115	31	7,4			1243	3045	
56	M	186	85	210	43							3086	
57	M	170	61	170	52	170	16			5,5	2472	3365	
58	F	162	57	160	39	140		6			1867	2688	
59	F	167	73	182	53	125	42	5,4			1852	2995	
60	M	165	79	186	58	145		5,4			2148	2545	
61	F	167	81,6	190	56	120		5,3			1811	4755	
62	M	172	67,3	179	60	160						2654	
63	F	171	64	175	49	120		5,0			1600		
64	M	184	71,5	193	21	95	31			4,2	1810	3	

AV	BC	Cyan	U	Inul	R P	R B	R V	P	P R	P A1
14054		121	108		667	1093	9 003	0 16	4 1	21,6
3664					410	707	13 918		3 7	22 1
	9 9	113			188	308	45 455	0 60	6 4	
3705					361	645			2 5	
3728		108			381	646	14 365	0 28	3 5	
	10 6	110			479	812	14 384	0 23	3 9	
4193					320	525	19 352		1 4	15 4
4453	10 4	87			405	614	17 199	0 21	5 3	
4247					442	804	13 333		12 7	14 6
5741		132	129		608	1086		0 21	14 0	
6448			139		555	1156	7 128	0 25	12 4	9 8
6706	12 3	140	128		575	1065	8 113	0,22	15 0	7,5
4335	9 1		75		313	559	19 893	0,24	12,3	6,3
3341		76	70		295	492		0 24	11 2	
	10 9	120	106		264			0 40	16 8	
6229			102		345	595	18 151	0 30	6 2	5 8
4990	9 8		166		775	1359	6 564	0 21	8 7	
4082									17 4	13 2
5573	13 6		130		980	1849	5 495	0 13	12 2	
5916			141		888	1531	6 108	0 16	11 8	13 7
4433	9,4	91	80		227	420	34 857	0 35	9 1	
4789	10 9		75		200	339	33 510	0 38	20 1	36 9
5342	14 7	143			743	1376	6 686	0 19	5 4	
5321		139			673	1202		0 21	8 3	
5608			123		360	600	22 667	0 34	10 6	31 9
4556		119			547	977	11 464	0 22	8 0	
4680	11 2	142			475	779	12 837	0 30	3 0	
4314	15 2	123			412	736	15 761	0 30	5 3	
6793	19 9								2 5	
4823	9 7	118			431	706	18 130	0 27	7 8	
	14 8	97			333	564	17 021	0 29	21 3	
5795			143		676	1186	6 408	0 21	17 4	9 8

Nr	Sex	Height	Weight	B S A	Age	M A P	Var	Dye	C O	Imp	T P R	P V	
33	F	160	59,8	162	19	123				5,4	1822	2392	
34	F	159	57,6	158	54	123				3,9	2523	2162	21
35	F	162	63,6	168	62	175		3,66			3825		
36	F	164	70	176	44		21					2223	2
37	F	163	72	176	45	116		3,7			2660	2274	2
38	F	163	68	174	49	146		4,33			2697		
39	F	164	72,9	179	53	127				7,2	1411	2517	
40	M	162	65	169	50	132		4,34			2439	2939	
41	F	165	65	171	61	134		8,8		5,7	1218	2336	2
42	M	180	68,2	186	36							3100	2
43	M	179,5	70	188	38	103	44			3 49	2361	3095	2
44	M	180	83	202	37	108						3621	2
45	F	154	48,8	144	39	139				2,99	3719	2341	2
46	F	163	53	156	34							2138	2
47	M	185	87,6	212	41	178		5,88			2422		
48	M	182	74,4	195	60	135	26			5,1	2118	3613	2
49	M	194	95	226	29	111		7,37			1210	2994	2
50	F	163	64,9	170	27							2327	2
51	M	182	76,3	197	27	127		7,2			1411	3288	2
52	M	182	79,4	200	29	114				5,28	1720	3431	2
53	F	158	65,2	166	68	183						2439	2
54	F	158	64	165	69	142				2,82	4028	2730	2
55	M	182	81	202	41	115	31	7,4			1243	3045	2
56	M	186	85	210	43							3086	2
57	M	170	61	170	52	170	16			5,5	2472	3365	2
58	F	162	57	160	39	140		6			1867	2688	2
59	F	167	73	182	53	125	42	5,4			1852	2995	2
60	M	165	79	186	58	145		5,4			2148	2545	2
61	F	167	81,6	190	56	120		5 3			1811	4755	2
62	M	172	67,3	179	60	160						2654	2
63	F	171	64	175	49	120		6,0			1600		
64	M	184	71,5	193	21	95	31			4,2	1810	3303	2

B V	E C V	Cyano O F R	Inulin	R P F	R B F	R V R	P F	P R C	P Aldo
6414	15 5	110		490	817	15 667	0 22	2 1	
4750			105	535	892	8 251	0 20	8 3	10 4
				731	1354			15	
		90		757	1402	6 847	0 12	16	
4214	13 2	112		595	1082	8 946	0 19	12	10 5
6342	16 9	148		598	1049	7 977	0 25	13	
4292								9 7	
6453	13 8	134		557	1051	11 418	0 24	7 0	
6385			128	576	1087	9 568	0,22	5 0	4 7
7115	12 4	122		660	1082	8 909	0,18	10 2	
5305			137	568	1014	8 205	0,24	7 9	15 2
5047	12 2	74	74	189	295		0,39	11 0	
5243	11 1		63	209	332	35 108	0 30	10 8	11 2
3077	10 9	107		336	560	20 714	0 32	5 7	
4611	13,9			507	805	12 522		5 5	
	13 9	124		453	719		0 27	5 0	5 6
5018	22 4							15 6	69 4
4523		145	102	391	611	17 610	0 26	14 6	13 8
4191	9 6	106	98	387	645	15 442	0 25	14 4	
5026			112	480	842	9 026	0 23	4 3	11 8
6084				477	782	13 095		3 4	9 0
5758			160	660	1200	8 600	0 24	15 7	7 5
6505	9 8	124		559	1055	7 386	0 22	9 1	
6522	15 9	141	125	513	933	11 790	0 24	9 6	
5008	16 7	134		709	1289	7 758	0 19	6 1	
5838		68		573	1042	7 793	0 12	5 5	
5251			125	561	1020	9 176	0 22	10 0	16 9
4228			107	333	608	16 132	0 32	9 0	34,2
4542	10 1		70	353	579	19 952	0 20	8 7	18 3
4284			103	432	708	12 090	0 24	7 5	7 0
		143		779			0 18	4 3	
3946			117	667	1112	7 698	0 18	5 4	1 2



Nr	Sex	Height	Weight	B S A	Age	M A P	Var	Dye	C O Imp	T P R	P V
65	M	182	86	207	50	160		5,61		2282	3720
66	M	176	57	170	29	92	30	8,7	8,8	846	2565
67	M	174	76	190	25		43				
68	M	174	78,2	193	26	120		6,0		1600	
69	M	175	80	195	28	121		5,58		1735	2360
70	M	187	90	216	34	104,6		7,15		1170	3615
71	M	178	66,5	183	32	97,3		7,1		1096	2618
72	M	174	90	204	43	150					3420
73	M	174	94	208	47	130			3,9	1507	3384
74	M	182	80	201	21	120,5		6,85		1407	3842
75	M	184	82	205	23	104		3,86	5,2	2155	2971
76	F	175	88,9	204	69						3028
77	F	172	86,6	200	70	145,7			6,33	1841	3198
78	F	154	47,6	143	36	145		5,35		2168	2000
79	F	159	82	184	44	126	28	5,2		1938	2951
80	F	159			44						
81	F	159	83	185	50	118,5		4,26	3,9	2225	3011
82	F	161	72,5	176	73	134,5		4,68		2299	2895
83	F	164	62	167	27	124,5		4,98	6,6	2000	2431
84	M	169	59	167	48	95			2,9	2621	2865
85	M	175	82,4	198	72	128			3,6	2844	3711
86	M	180	81 2	200	26	129			5,28	1955	2994
87	M	172	75	188	39	97,4		6,62		1177	3838
88	M	184	82,5	206	53	137,5		5,05		2178	3783
89	M	176	90	206	35	125	37	7,4		1351	2955
90	M	176	87	204	37	101,5		6 5		1249	3211
91	M	176	94	207	41	117			5,8	1613	2888
92	M	175	68	183	45	122			7,0	1394	2452
93	F	157	83 2	184	55	144,4		3,62	3,69	3191	2680
94	F	160	56	157	47	107			4 2	2038	2485
95	F	165	65,5	172	24						
96	F	165	57	162	29	107			4,0	2140	2407

B V	E C V	Cyano ■ F R <sub>2</sub>	Inulin	R P F	R B F	R V R	P F	P R C	P Alda
6613				608	1067	10 047	-	8,8	
4915	12 7	114		515	888	11 712	0 22	2 5	
4361	10 ■	133		671	1137	8 443	0,20	5,3	
4661		85	70	237	389	28 792	0,30	8 1	12 6
		128		387	717	13 389	0,33	3,2	
		141		359	668		0 39	9,1	
4976			82	172	273	42 491	0 48	26,5	24 7
5352	14 1	164		783	1450	6 621	0,21	7 5	
5672	14 6							10 6	
5974			138	892	1538	6 242	0 15	10 9	16 6
5616			114	541	984	9 959	0,21	12 5	6 5
3823	11 1	121	105	540	871	10 608	0 19	8 0	
3321	10 7	107	85	361	547	18 501	0 24	5 5	
6387	10,9		122	555	1009	9 911	0 22	16 9	12 1
4502				499	846	11 537		11 3	7 1
7311	10,9		55	92	146	76 438	0 60	15 2	66 3
5009	9 6							8 6	16 0
3825	9 8	100	99	491	767		0 20	3 5	
	10 6		70	129	215	55 814	0 54	7 8	
3582			53	115	202	65 347	0 46	12 2	39 4
4868	7 9		98	261	458	20 961	0,36	4 1	17 9
3991		65		268	454		0 24		
3531	8 0	98		411	663	15 324	0 24	6 4	
4224			100	487	812	11 881	0 21	7 9	12 7
4491				415	883			10	
4224	12 4	112		355	645	17 364	0 32	4 3	
4074	11 3	115		585	929	8 611	0 20	3 6	
6822				773	1356	7 906			
		167		763	1339		0 22	5 3	
6732			128	540	982	9 939	0 24	13 4	20 4
3448				328	547	16 819		13 3	
		75		229	352		0 33	2 6	

Nr	Sex	Height	Weight	B S A	Age	M A P	Var	Dye	C O Imp	T P R	P V
97	M	182	85,9	207	43	134	34	7,2		1489	3968
98	F	167	74	183	50	130	32	5,07		2051	2900
99	M	174	70	184	31	120	33	7,1		1352	2660
100	F	163	70	175	64	140			5,1	2196	2890
101	M	178	84	202	59	120					
102	M	178	84	202	60						
103	M	167	60	167	58	145			5,5	2109	3334
104	M	186	99	224	45	120		7,8		1231	3104
105	M	183	93	215	47	124		7,73		1283	3290
106	M	183	94,5	216	50	120			7,1	1352	3405
107	M	177	77	194	58	122,5		4,08		2402	3145
108	F	171	68,5	180	25	115,5		4,2		2200	2370
109	F	163	63	168	51	126,5		6,55		1545	2059
110	M	183	85,8	208	43	125			5,7	1754	3385
111	F	171	73,3	185	45	122			5,1	1914	2431
112	M	172	79	192	57	139,5		3,44	4,7	3244	4460
113	M	173	67,5	180	35						2805
114	F	165	55,5	160	30						2295
115	F	156	59	160	50	150		4,46		2691	
116	F	154	63	161	57	165					2042
117	F	160	64,4	167	53	120			4,4	2182	2580
118	F	165	56,3	161	52						2594
119	F	165	57	162	40	127		4,2		2419	2295
120	F	165	55,5	160	45	120			6,1	1574	2492
121	M	163	73	179	52						2111
122	M	162	68	173	55	140	31	3,9		2872	2323
123	F	159	70	172	35	100	43	6,95		1151	2770
124	M	189	85	212	43	134		6,5		1649	4093
125	M	189	84,5	212	44						
126	M	189			50	122			4,2	2324	3568
127	F	161	59,2	162	43	115	34	5,2		1769	2000
128	F	161	59,3	162	43						

B V	E C V	Cyano D F R <sub>2</sub>	Inulin	R P F	R B F	R V R	P F	P R C	P Aldo
6613				608	1067	10 047	-	8 8	
4915	12,7	114		515	888	11 712	0 22	2 5	
4361	10,0	133		671	1137	8 443	0 20	5 3	
4661		85	70	237	389	28 792	0,30	8,1	12,6
		128		387	717	13 389	0 33	3 2	
		141		359	668		0 39	9 1	
4976			82	172	273	42 491	0 48	26 5	24 7
5352	14 1	164		783	1450	6 621	0 21	7 5	
5672	14,6							10 6	
5974			138	892	1538	6 242	0 15	10 9	16 6
5616			114	541	984	9 959	0 21	12 5	5 5
3823	11 1	121	105	540	871	10 608	0 19	8 0	
3321	10 7	107	85	361	547	18 501	0 24	5 5	
6387	10 9		122	555	1009	9 911	0 22	16 9	12 1
4502				499	846	11 537		11 3	7 1
7311	10 9		55	92	146	76 438	0 60	15 2	66 3
5009	9 6							8,6	16 0
3825	9 8	100	99	491	767		0,20	3 5	
	10 6		70	129	215	55 814	0 54	7 8	
3582			53	115	202	65 347	0,46	12 2	39 4
4868	7,9		98	261	458	20 961	0 36	4 1	17 9
3991		65		268	454		0 24		
3531	8 0	98		411	663	15 324	0 24	6,4	
4224			100	487	812	11 881	0 21	7 9	12 7
4491				415	883			10	
4224	12 4	112		355	645	17 364	0 32	4 3	
4074	11 3	115		583	929	8 611	0 20	3 6	
6822				773	1356	7 906			
		167		763	1339		0 22	5 3	
6732			128	540	982	9 939	0 24	13 4	20 4
3448				328	547	16 819		13 3	
		75		229	352		0 33	2 6	

Nr	Sex	Height	Weight	B S A	Age	M A P	Var	Dye	C O	Imp	T P R	P V
97	M	182	85,9	207	43	134	34	7,2			1489	3968
98	F	167	74	183	50	130	32	5,07			2051	2900
99	M	174	70	184	31	120	33	7,1			1352	2660
100	F	163	70	175	64	140				5,1	2196	2890
101	M	178	84	202	59	120						
102	M	178	84	202	60							
103	M	167	60	167	58	145				5,5	2109	3334
104	M	186	99	224	45	120		7,8			1231	3104
105	M	183	93	215	47	124		7,73			1283	3290
106	M	183	94,5	216	50	120				7,1	1352	3405
107	M	177	77	194	58	122,5		4,08			2402	3145
108	F	171	68,5	180	25	115,5		4,2			2200	2370
109	F	163	63	168	51	126,5		6,55			1545	2059
110	M	183	85,8	208	43	125				5,7	1754	3385
111	F	171	73,3	185	45	122				5,1	1914	2431
112	M	172	79	192	57	139,5		3,44		4,7	3244	4460
113	M	173	67,5	180	35							2805
114	F	165	55,5	160	30							2295
115	F	156	59	160	50	150		4,46			2691	
116	F	154	63	161	57	165						2042
117	F	160	64,4	167	53	120				4,4	2182	2580
118	F	165	56,3	161	52							2594
119	F	165	57	162	40	127		4,2			2419	2295
120	F	165	55,5	160	45	120				6,1	1574	2492
121	M	163	73	179	52							2111
122	M	162	68	173	55	140	31	3,9			2872	2323
123	F	159	70	172	35	100	43	6,95			1151	2770
124	M	189	85	212	43	134		6 5			1649	4093
125	M	189	84,5	212	44							
126	M	189			50	122				4,2	2324	3568
127	F	161	59,2	162	43	115	34	5,2			1769	2000
128	F	161	59,3	162	43							

B V	E E V	Cyano G F R.	Inulin	R P F	R B F	R V R	F F	P R C	P Aldo
	10 3							17 2	
39259		72	81	289	535	23 028	0 28	15 9	12 B
4216	11 9	99	127	329	621		0,39	8 1	
4818	13 9	155		1023	1764	4 762	0 15	8	
5587			101	339	605	18 282	0 30	15 8	15 B
3834	7 4							20 8	
4826	10 B		163	528	866	12 776	0 31	14 1	6 9
4504			100	549	980	9 796	0 18	11 4	5 1
		82		308	550		0 27	40	
5395	12 6	107	118	493	836		0 24	7 B	
		152	115	559	1016		0 21	22 2	
3379	9 4		86	209	299	36 120	0 41	6 8	7 3
5343				241	389				
4956			114	492	863	12 051	0 23	22 4	33 8
3686			106	539	914	10 066	0 20	8 3	12 2
5117	10 B	165		773	1487	5 649	0 21	6 7	
4361	7 0							3 8	
3162			87	479	785	10 191	0 18	13 2	10 1
4925				619	1263	7 918		12	
	14 8	125		425	708	19 774	0 29	1 8	
5045			62	205	347	31 170	0 30	11 8	5 1
4510			105	440	710	11 493	0 24	5 7	43 7
4919				847	1366	6 676			
4583	12 B	154		828	1355	9 588	0 19	5 0	
5100	9 B	118		458	777	10 656	0 26	9 7	43 1
4915	13 5	185		599	1175		0 31	9 8	
3932								15 B	
4792			106	368	566	20 071	0 29	6 6	44 9
3567		94	92	425	733	12 715	0 22	3 6	10 6
3456	14 5	166	113	567	930	13 763	0 20	3 6	
3495	8 9	66	87	440	733	11 405	0 20	13 2	

Nr	Sex	Height	Weight	B S A	Age	M A P	Var	Dye	C O Imp	T P R	P V
129	M	164			34	131,5		7,55		1393	
130	F	161	60	163	50	154		3,47	5,43	3550	5000
131	M	172	74	187	63						2108
132	M	180	74	193	24	105	50	9,1		923	
133	M	179	75	193	24	105		7,6		1105	3180
134	M	173	75,8	189	58	121			5,1	2115	3073
135	F	168	62	170	31	124,3		5,28		1883	2684
136	F	168	63,4	172	34	138,3		4,82	5,64	2295	2944
137	M	167	64	172	18	120	26		7,3	1315	2432
138	F	163	63,4	168	64						
139	M	186	79,3	203	30						2967
140	M	186	87	212	64						
141	F	156	55	154	52	135			4,1	2634	2298
142	F	171	60,5	170	47						3473
143	F	164	56	160	44	130			5,3	1962	2825
144	F	150	56	151	36	115			4,9	1877	2175
145	M	183	82,3	204	28	105	37	7,8		1077	3070
146	F	163	47	148	50	158		2,62		4824	2442
147	M	155	57	155	58	100	16		3,0	2667	1929
148	M	158	68	170	53	125	37	6,3		1587	2758
149	M	181	82,7	203	63	175	12	5,85		2393	
150	F	164	60,7	165	57	135,2			4,18	2588	2674
151	F	152	61	158	58	102					2751
152	F	165	60	166	28	114	48	7,6		1200	3148
153	F	174	71	185	44	160	30	7 85		1631	2933
154	M	180	75	194	36	103,5		7 9		1048	2805
155	M	171	91,8	204	43						2605
156	F	161	60	163	47	131		3,48		3011	2359
157	F	166	69,5	177	46	142			4,2	2705	3163
158	F	155	51	148	47	116	5	3 66	3,7	2546	2069
159	M	180	88	208	60	160					2177
160	M	168	51	157	24	104,5		5 92		1412	1957

B V	E C V	Cyano O P R <sub>2</sub>	Inulin	R P F	R B F	R V R	F F	P R C	P Aldo
		160		608	1105		0 26	5 8	23 3
4359		105		653	1146	5 585	0,16	5 5	
6678	15,7	175		627	1140	8 421	0,28	3 4	
6820	12 5	155		632	1170	8 547	0 25	6 4	
6206								23	
4215				633	1055			14 9	
4256			108	455	784	15 306	0 24	2 2	18 5
5665			122	500	926	8 639	0 24	8,7	14 8
4790								17 1	
4786	7 4	117	116	521	883	9 875	0 22	11 6	18,2
5305	12 6	125		577	1089	9 550	0 22	5 3	
4852									
4784		134		465	861	12 544	0 29	2 4	
		117	110	455	812		0 24	8 6	
5675	8 6	125	118	376	684	15 883	0 31	8 6	21 4
4202	8 7							22 6	
4098	8 9	88	75	305	555	22 342	0 25	5 8	
4716				427	712	13 034		2 3	8 4
4300	10 2	93		351	585	17 915	0 26	8 0	
2825	9 8	95		484	849	12 250	0 20	5 3	
6758	10 5	146	158	420	712	13 371	0 35	8 6	
3702	9 6	93	74	363	648	19 753	0 20	3 6	
4271	7 7		64	307	512	19 656	0 21	8 6	30 8
5272			110	312	578	16 609	0 35	9 7	21 5
5095	16 5	155		593	1059	10 576	0 26	5 4	
5515	12 8	135		449	748	13 829	0 30	2 3	
5537	12 9	108		463	874	12 082	0 23	10 0	
6528		132	135	339	556	21 367	0 40	5 6	2 1
3560	9 3	86	80	396	660	13 939	0 20	7 4	
4356			101	444	783	12 218	0 23	9 3	8 0
5333	16 2		127	587	962	14 012	0 22	9 0	15 2
5929	13 9	151		456	894	11 544	0 33	11 1	



Nr	Sex	Height	Weight	B S A	Age	M A P	Var	Dye	C O Imp	T P R	P V
161	M	184	104	227	53						
162	M	162	65	169	35	80	38	6,62		967	2790
163	M	179	84	202	54	120		5,2		1846	3940
164	M	179	81,5	200	55	125		6,4		1562	3751
165	M	178	84,1	202	56						3289
166	F	167	70	178	53						2571
167	F	163	58,6	162	50	150	22		5,0	2400	2290
168	M	179	83,4	202	49	100	28		3,7	2162	3229
169	F	158	63	164	70						2874
170	M	171	78,5	191	43	109		4,79		1820	2680
171	M	182	74	195	23	130	46	5,8		1793	2918
172	M	174	69,5	183	54						2911
173	M	172	67,5	180	55	135	31	5,85		1846	2918
174	M	173	75	189	59						
175	F	160	56,8	158	41	135,8		4,29	5,7	2532	2894
176	M	161	63	166	51						2395
177	M	156	60,4	160	58	155					2254
178	F	163	64	169	47	116	28	4,6		2017	2924
179	F	162	65,8	170	49	131					2752
180	F	163	60	164	23	130	29	4,3		2419	1780
181	M	186	82	206	45	119		6,87		1386	4055
182	F	159	52	152	30	160		4,6		2783	2184
183	F	166	65,7	173	57	125,8		5 13	4,1	1962	2349
184	M	168	70	179	70	120		5,35	5,1	1794	2847
185	M	183	60	208	60	140	40	7,1		1577	2955
186	M	183	63	200	63	129,3		4,71		2196	3309
187	M	184	64	204	64	132		5,99		1763	2990
188	M	183	66	206	66	148,5		4,04		2941	3917
189	F	162	22	152	22	115					2207
190	F	162	24	157	24	115			4,6	2000	2483
191	F	163	53	190	53	168,5	18		3,7	3643	3093
192	M	182	55	226	55	129		3,62		2851	3083

B V	E C V	Cyano G P R <sub>2</sub>	Inulin	R P F	R B F	R V R	P F	P R C	P Aldo
		160		608	1105		0 26	5 8	23 3
4359		105		653	1146	5 585	0 16	5 5	
6678	15 7	175		627	1140	8 421	0,28	3 4	
6820	12,5	155		632	1170	8 547	0 25	6 4	
6206								23	
4215				633	1055			14 9	
4256			108	455	784	15 306	0 24	2 2	18 5
5665			122	500	926	8 639	0 24	8 7	14 8
4790								17 1	
4786	7 4	117	116	521	883	9 875	0 22	11 6	18 2
5305	12 6	125		577	1089	9 550	0 22	5 3	
4852									
4784		134		465	861	12 544	0,29	2 4	
		117	110	435	812		0 24	8 6	
5675	8,6	125	118	376	684	15 883	0 31	8 6	21 4
4202	8 7							22 6	
4098	8 9	88	75	303	553	22 342	0 25	5 8	
4716				427	712	13 034		2 3	8 4
4300	10 2	93		351	585	17 915	0 26	8 0	
2823	9 8	93		484	849	12 250	0 20	3 3	
6758	10 5	146	158	420	712	13 371	0 35	8 6	
3702	9 6	93	74	363	648	19 753	0 20	3 6	
4271	7 7		64	307	512	19 656	0 21	8 6	30,8
5272			110	312	578	16 609	0 35	9 7	21 5
5095	16 5	155		593	1059	10 576	0 26	5 4	
5515	12 8	135		449	748	13 829	0 30	2 3	
5537	12 9	108		463	874	12 082	0 23	10 0	
6528		132	135	339	556	21 367	0 40	5 6	2 1
3560	9 3	86	80	396	660	13 939	0 20	7 4	
4356			101	444	783	12 218	0 23	9 3	8 0
5333	16 2		127	587	962	14 012	0 22	9 0	15 2
5929	13 9	151		456	894	11 544	0 33	11 1	

Nr	Sex	Height	Weight	B S A	Age	M A P	Var	Dye	C O	Imp	T P R	P V
161	M	184	104	227	53							
162	M	162	65	169	35	80	38	6,62			967	2790
163	M	179	84	202	54	120		5,2			1846	3940
164	M	179	81,5	200	55	125		6,4			1562	3751
165	M	178	84,1	202	56							3289
166	F	167	70	178	53							2571
167	F	163	58,6	162	50	150	22		5,0		2400	2290
168	M	179	83,4	202	49	100	28		3,7		2162	3229
169	F	158	63	164	70							2874
170	M	171	78,5	191	43	109		4,79			1820	2680
171	M	182	74	195	23	130	46	5,8			1793	2918
172	M	174	69,5	183	54							2911
173	M	172	67,5	180	55	135	31	5 85			1846	2918
174	M	173	75	189	59							
175	F	160	56,8	158	41	135,8		4,29	5,7		2532	2894
176	M	161	63	166	51							2395
177	M	156	60,4	160	58	155						2254
178	F	163	64	169	47	116	28	4,6			2017	2924
179	F	162	65,8	170	49	131						2752
180	F	163	60	164	23	130	29	4,3			2419	1780
181	M	186	82	206	45	119		6,87			1386	4055
182	F	159	52	152	30	160		4,6			2783	2184
183	F	166	65,7	173	57	125,8		5,13	4,1		1962	2349
184	M	168	70	179	70	120		5,35	5,1		1794	2847
185	M	183	60	208	60	140	40	7,1			1577	2955
186	M	183	63	200	63	129,3		4,71			2196	3309
187	M	184	64	204	64	132		5,99			1763	2990
188	M	183	66	206	66	148,5		4 04			2941	3917
189	F	162	22	152	22	115						2207
190	F	162	24	157	24	115			4,6		2000	2483
191	F	163	53	190	53	168,5	18		3,7		3643	3093
192	M	182	55	226	55	129		3,62			2851	3083

B V	K C V	Cyano O F R <sub>u</sub>	Inulin	R P F	R B F	R V R	F F	P R C	P Aldo
5323									
		110		436	838	10 979	0 25	12 5	
5002			142	607	1104	7 971	0 23	9 5	1 9
5573	8 7		90	352	618	16 828	0 26	13 6	10 3
6415	12 3		110	427	854	12 178	0 26	3 5	
6743			116	433	787	12 198	0 27	7 0	3 4
5438			156	580	1094	8 775	0 27	4 2	8 6
5530	12 1							5 1	11 7
5221		133		752	1367	6 000	0 18	8	
4540			102	301	528	20 000	0 34	2 0	
5392			101	423	769	12 484	0 24	13 9	6 3
3085	9 6	85		371	580	16 000	0 23	5 1	8 5
3984		124		600	952	12 605	0 21	3 1	
5140			114	368	634	14 132	0 31	8 9	18 5

Nr	Sex	Height	Weight	B S A	Age	M A P	Var	Dye	C O	Imp	T P R	P V
193	M	172	31	193	31		24					2981
194	M	174	33	195	33	143		7,0			1634	
195	M	173	35	200	35	115		4,6			2000	
196	M	174	40	204	40	110				4,6	1913	2851
197	M	179	73	181	73	130				5,8	1793	2842
198	M	177	45	195	45	130						3336
199	M	177	47	184	47	120	22			4,2	2286	3641
200	M	172	47	196	47	120				6,0	1600	3263
201	M	176	54	191	54	138,5		5,08			2181	3152
202	M	194	25	228	25	117,9		5,93			1591	2924
203	F	160	69	174	69	132				4,8	2200	2588
204	M	174	50	184	50	120				5,4	1778	2804
205	F	156	36	151	36	116	34	5,3			1751	2067
206	F	157	50	154	50	150	29	4,82			2490	2510
207	M	163	58	178	58	112	28					2930

B V	B C V	Cyano G F R <sub>2</sub>	Inulin	R P F	R B F	R V R	P F	P R C	P Aldo
5323									
		110		436	838	10 979	0 25	12 6	
5002			142	607	1104	7 971	0 23	9 5	1 9
5573	8 7		90	352	618	16 828	0 26	13 6	10 3
6415	12 3		110	427	854	12 178	0 26	3 6	
6743			116	433	787	12 198	0 27	7 0	3 4
5438			156	580	1094	11 775	0 27	4 2	8 6
5530	12 1							6 1	11 7
5221		133		752	1367	6 000	0 18	8	
4540			102	301	528	20 000	0 34	2 0	
5392			101	423	769	12 484	0 24	13 9	6 3
3085	9 6	85		371	580	16 000	0 23	6 1	8 5
3984		124		600	952	12 605	0 21	3 1	
5140			114	368	634	14 132	0 31	8 9	18 5



Table A 2.

Individual data presented per m<sup>2</sup> for 26 patients with uncomplicated essential hypertension during follow-up



# Haemodynamic data of uncomplicated hypertension during the follow-up study

Study	Age	Sex	MAP mm Hg	PA ml/m	RPF ml/min/m <sup>2</sup>	RVR dyn sec cm <sup>-5</sup> /m <sup>2</sup>	PRC ng/ml hr
INITIAL	25	M	110	-	514	10263	
FINAL	29.5		91	1509	314	14003	8.1
INITIAL	27	M	125	1661	434	11979	13.7
FINAL	30		117	1707	447	12294	11.7
INITIAL	31.4	F	130	1646	399	1881	8.8
FINAL	35		128	174	223	28090	11.6
INITIAL	31.5	F	113	1317	3.1	15661	6.9
FINAL	37		114	1508	776	14847	11.1
INITIAL	35	M	117	1449	355	1466	7.6
FINAL	4		11	1311	765	17474	10.0
INITIAL	36	M	94	1658	178	12839	13.6
FINAL	38		99	1638	785	13173	1.3
INITIAL	37	M	100	1371	339	14315	7.0
FINAL	43		104	1411	310	14799	7.3
INITIAL	39	F	110	1497	366	14171	5.1
SECOND	4		126	1380	341	18108	7.3
FINAL	45.5		126	1714	319	18804	3.4
INITIAL	40.7	F	131	1408	57	4579	6.8
FINAL	45.3		131	1558	304	30431	7.8
INITIAL	44	F	148	1604	775	76798	5.5
FINAL	50.6		140	1619	159	44176	13
INITIAL	44	F	135	1285	184	17196	
SECOND	5		139	1763	30	31284	4.9
FINAL	53.5		126	1406	177	34360	1.4
INITIAL	44	M	130	1676	77	70193	8.4
FINAL	47		138	1643	280	1016	4.9

Hemodynamic data of uncomplicated essential hypertension during the follow-up study

Study	Age	Sex	SIAP mm Hg	PA mm Hg	CO ml/min/m <sup>2</sup>	SVR dyn sec. cm <sup>5</sup> /m	Plasma ng/ml hr
INITIAL	45.8	M	130	151	33	1904	4.2
FINAL	47.3		120	142	38	1529	9.3
INITIAL	41.6	M	153	193	33	1031	5.9
FINAL	40.5		146	169	36	2618	11.8
INITIAL	41.9	M	100	180	31	1566	7.5
FINAL	48		113	158	38	1834	5.9
INITIAL	45.8	M	135	171	46	1933	2.6
FINAL	47.8		135	179	29	2540	5.4
INITIAL	47.7	F	120	173	25	2561	3
FINAL	51		126	176	21	1800	4.5
INITIAL	48.3	M	121	188	17	3161	7.4
FINAL	49.4		127	176	15	3786	5.0
INITIAL	1	F	140	187	81	5698	9.1
FINAL	48		166	168	70	6631	11
INITIAL	3	M	145	179	31	1682	10
FINAL	41		130	175	23	2091	9
INITIAL	60.7	M	125		76	7010	5.2
SECOND	61		120	148	28	2063	1.6
THIRD	62		112	147	29	2273	10.9
FINAL	66.1		145	161	29	2477	12.5



### Table A 3

Individual data for 5 patients during follow-up in whom the course was complicated by myocardial infarction.



# **Acta Medica Scandinavica**

**Supplementum 623**

***New aids in diagnosing acute  
myocardial infarction***

**Edited by Bengt W Johansson**



# **New aids in diagnosing acute myocardial infarction**

**Edited by Bengt W Johansson**



# Acta Medica Scandinavica

originally published as *Nordiskt Medicinskt Arkiv* was founded in 1869 by Professor Axel Key MD. In 1901 (from volume 34) this journal was divided into a medical and a surgical section. Since 1919 (from volume 52) the medical section has been published under the name of *Acta Medica Scandinavica*.

## *Acta Medica Scandinavica*

publishes papers on general medicine mainly from Denmark, Finland, Iceland, Norway, Sweden and the Netherlands. Short preliminary reports (not exceeding two pages) will be published at short notice. The papers are published in English, French or German. *Acta Medica Scandinavica* is published on a non-profit basis.

## *Subscriptions*

to *Acta Medica Scandinavica* (two volumes of six numbers each annually) include free supplements to the current volumes.

## *Subscription Rates*

Per annum = two volumes.

In Denmark, Finland, Iceland, Norway, Sweden and the Netherlands: Sw kr 300 incl. postage. Swedish subscribers add VAT.

Other countries Sw kr 345 incl. postage.

## *Chief Editor*

Professor Jan G Waldenström, MD  
*Acta Medica Scandinavica*  
Kungsgatan 54  
S-111 35 Stockholm, Sweden

## *Editorial Office*

*Acta Medica Scandinavica*  
Kungsgatan 54  
S-111 35 Stockholm, Sweden  
(All correspondence concerning manuscripts and editorial matters)  
Telephone 08/21 77 63

## *Subscription Distribution and Advertising*

The Almqvist & Wiksell Periodical Company  
Gamla Brogatan 26, Box 62  
S-101 20 Stockholm 1 Sweden

## *Printers*

Almqvist & Wiksell Tryckeri AB  
S-751 81 Uppsala, Sweden

# **New aids in diagnosing acute myocardial infarction**

**Edited by Bengt W Johansson**

# Acta Medica Scandinavica

originally published as *Nordiskt Medicinskt Arkiv* was founded in 1869 by Professor Axel Key MD. In 1901 (from volume 34) this journal was divided into a medical and a surgical section. Since 1919 (from volume 52) the medical section has been published under the name of *Acta Medica Scandinavica*.

## *Acta Medica Scandinavica*

publishes papers on general medicine mainly from Denmark, Finland, Iceland, Norway, Sweden and the Netherlands. Short preliminary reports (not exceeding two pages) will be published at short notice. The papers are published in English, French or German. *Acta Medica Scandinavica* is published on a non-profit basis.

## *Subscriptions*

to *Acta Medica Scandinavica* (two volumes of six numbers each annually) include free supplements to the current volumes.

## *Subscription Rates*

Per annum = two volumes.  
In Denmark, Finland, Iceland, Norway, Sweden and the Netherlands: Sw kr 300 incl. postage. Swedish subscribers add VAT.  
Other countries Sw kr 345 incl. postage.

## *Chief Editor*

Professor Jan G. Waldenström, MD  
*Acta Medica Scandinavica*  
Kungsgatan 54  
S-111 35 Stockholm, Sweden

## *Editorial Office*

*Acta Medica Scandinavica*  
Kungsgatan 54  
S-111 35 Stockholm, Sweden  
(All correspondence concerning manuscripts and editorial matters)  
Telephone 08/21 77 63

## *Subscription Distribution and Advertising*

The Almqvist & Wiksell Periodical Company  
Gamla Brogatan 26, Box 62  
S-101 20 Stockholm 1, Sweden

## *Printers*

Almqvist & Wiksell Tryckeri AB  
S-751 81 Uppsala, Sweden

# **New aids in diagnosing acute myocardial infarction**

**Edited by Bengt W Johansson**

*Printed in Sweden  
by  
Malmö Centraltryckeri  
Malmö 1978*

# CONTENTS

## GENERAL LECTURES

J. Aikesson: Electrocardiographic mapping of ischaemic myocardial insult	7
R. Nordlander: Enzymes in acute myocardial infarction. Diagnosis with special reference to creatine kinase MB isoenzyme	18
J. Lersøm: Radionuclides in acute myocardial infarction	27
B. Scherstén, D. Urrung and G. Jonsson: Myoglobin	38
N. H. Sternby: Morphological diagnosis of early acute myocardial infarction	43

## FREE LECTURES

P. Grande, C. Christensen and A. Pedersen: Creatine kinase MB isoenzyme in diagnosis of acute myocardial infarction	48
E. Lorentzen, D. Scott and H. Steensland: Serial CPH determinations after acute myocardial infarction. The possible use of this technique in objective evaluation of myocardial infarction treatment	53
P. F. Høiland-Carlson, J. Budskjær, J. Borchum-Hertz, O. H. Sørensen: The predictive value of myocardial scintigraphy with $^{99m}\text{Tc}$ -pyrophosphate in diagnosing acute myocardial infarction	55
K. Thygesen, M. Hørdér, B. Lyager-Nielsen and P. Hyltoft-Petersen: The variability of ST segment - the early phase of acute myocardial infarction	61
J. Heikkilä and M. S. Nieminen: Rapid monitoring of regional myocardial ischaemia with echocardiography and ST segment shifts in man	71
J. Godtfredsen, P. Kryger and H. Lublin: Left ventricular function after myocardial infarction. Relation between systolic time intervals and quantitative ischaemic ECG changes	96
K. Kälendörff, F. Pedersen, E. Christensen and I. Gad: Rocket immunoelectrophoresis of myoglobin in urine in patients with myocardial infarction	103

*Printed in Sweden  
by  
Malmö Centr tryckeri  
Malmö 1978*

# INTRODUCTION

The diagnosis of acute myocardial infarction is based on the patient history, electrocardiographic finding, serum enzymes, and the finding of a necrotic myocardium at autopsy. For it to be reliable, one or more of these criteria are needed. Early diagnosis is important for several reasons. Most arrhythmic complications appear during the early stage of the infarction. The earlier the diagnosis, the earlier the monitoring can begin. Experimental data indicate that infarct size can be reduced by mechanical assistance or pharmacological interventions. It is not certain that these experimental data can be transferred to clinical practice, but early intervention is essential for a successful result. Early exclusion of acute infarction will save expensive hospital beds.

In recent years, new aids for diagnosing acute myocardial infarction have appeared. ST mapping, isoenzymes, radionuclides, determination of myoglobin in urine and serum, and staining and chemical procedures applied to autopsy material. These new aids were a major topic at the Nordic Congress of Cardiology, Ystad, Sweden, August 26–27, 1977. Introductory reviews of them were presented. Voluntary papers, directly relevant, were selected. These are published in the present volume, as is also the closing panel discussion, which sought to adapt these new aids to clinical practice, based on our present knowledge.

I gratefully acknowledge the generosity of the sponsors for making this publication possible.

*Bengt W. Johansson*  
Heart Section  
General Hospital  
MALMÖ SWEDEN



# PANEL DISCUSSION

Bengt W Johansson	106
L. Ljungdahl W Gerhardt and S Hofvendahl Some pitfalls in the determination of S-creatine kinase B-subunit activity with an immunoinhibition method	108
Bengt W Johansson	113
A. Kontinen and K Ojala Accurate determination of serum ASAT isoenzymes	113
A. Kontinen Creatine kinase isoenzymes in the confirmation of acute myocardial infarction	115
Bengt W Johansson	117
S Hofvendahl, W Gerhardt, L. Ljungdahl and J S Olsen Are predictive values from different patient materials comparable?	117
Bengt W Johansson	120
J Lessem Myocardial scintigraphy in an emergency room	121
J Fischer Hansen J Lessem, B Scherstén, J Lessem, P F Houlund-Carlson J Lessem S Persson J Lessem E. Sandøe, J Lessem, B W Johansson, J Lessem,	122
B W Johansson B Scherstén J Lessem V Hansteen, J Hjelshus, B. W Johansson	123
S Hofvendahl A Pedersen, E. Lorentsen C Müller S Ström J Lessem	124
K. E. Grevin, L. Malmberg B Scherstén M. Horder G Björck	125
Bengt W Johansson	126
G E. Voigt The diagnostic of fresh ischaemic lesions in forensic pathology	126

# INTRODUCTION

The diagnosis of acute myocardial infarction is based on the patient history, electrocardiographic finding, serum enzymes, and the finding of a necrotic myocardium at autopsy. For it to be reliable, one or more of these criteria are needed. Early diagnosis is important for several reasons. Most arrhythmic complications appear during the early stage of the infarction. The earlier the diagnosis, the earlier the monitoring can begin. Experimental data indicate that infarct size can be reduced by mechanical assistance or pharmacological interventions. It is not certain that these experimental data can be transferred to clinical practice, but early intervention is essential for a successful result. Early exclusion of acute infarction will save expensive hospital beds.

In recent years, new aids for diagnosing acute myocardial infarction have appeared: ST mapping, isoenzymes, radionuclides, determination of myoglobin in urine and serum, and staining and chemical procedures applied to autopsy material. These new aids were a major topic at the Nordic Congress of Cardiology, Ystad, Sweden, August 26–27, 1977. Introductory reviews of them were presented. Voluntary papers, directly relevant, were selected. These are published in the present volume, as is also the closing panel discussion, which sought to adapt these new aids to clinical practice, based on our present knowledge.

I gratefully acknowledge the generosity of the sponsors for making this publication possible.

*Bengt W. Johansson*  
Heart Section  
General Hospital  
MALMÖ SWEDEN



# Electrocardiographic mapping of Ischaemic myocardial insult

John K Kjekshus

University of Oslo Dept. of Medicine B Rikshospitalet, OSLO NORWAY

Recent research has shown that the extent of myocardial infarction is not determined at the onset of the coronary occlusion. A varying lapse of time takes place before irreversible damage is established. During this period of reversible myocardial injury some appropriate interventions can favourably influence the final outcome of the pathological process (1). Because the prognosis of the myocardial insult is dependent on the size of the infarct (2), the testing of therapeutic approaches designed to reduce infarct size has become a major challenge for clinicians. The ischaemic injury is liable to extension as well as reduction in the reversible period dependent on various interacting haemodynamic and metabolic factors that will modify the effect of interventions. For instance a decrease in myocardial oxygen requirement obtained by reduction of after load might also result in reduction of coronary perfusion pressure and increase in heart rate. The resultant effect on the ischaemic area could therefore be unpredictable. Method for quantitating infarct size is consequently indispensable in the treatment of patients with acute ischaemic insults of the myocardium. Current techniques in use for measuring the ischaemic injury include

- 1) grading of the ischaemic pain (3)
- 2) analysis of cumulated creatine kinase (CK) time-activity curves (4, 5)
- 3) adenoside imaging (6)

- 4) anaerobic metabolites in coronary sinus (7)

- 5) precordial ST-segment mapping (8)

- 6) precordial QR-mapping (9)

The use of the electrocardiogram for infarct sizing has obvious advantages. It is direct, simple, inexpensive, and non-invasive.

## Animal experiments

### ST-segment elevation

The relation between ST-segment elevation and coronary occlusion was probably first recognized in 1920 (10). Later Raab (11) demonstrated that epicardial ST-segment changes during coronary constriction were augmented by catecholamine stimulation of the myocardium. Experiments initiated in San Diego by Maroko et al. (1) showed that epicardial mapping of ST-segment changes was quite useful for indexing acute ischaemic injury of the myocardium underlying the exploring electrode (Fig. 1). Within 30 seconds after coronary artery occlusion, ST-segment elevation appears in the area of ischaemia indicated by cyanosis and systolic bulging. Areas outside the ischaemic zone do not show ST-segment elevation. Accordingly the size of the acute ischaemic region can be outlined by the number of epicardial positions displaying elevation. The height of the elevation was taken to indicate the magnitude of ischaemic injury and the



# Electrocardiographic mapping of Ischaemic myocardial insult

John K. Kjekshus

University of Oslo, Dept. of Medicine B Rikshospitalet, OSLO NORWAY

Recent research has shown that the extent of myocardial infarction is not determined at the onset of the coronary occlusion. A varying lapse of time takes place before irreversible damage is established. During this period of reversible myocardial injury some appropriate interventions can favourably influence the final outcome of the pathological process (1). Because the prognosis of the myocardial insult is dependent on the size of the infarct (2), the testing of therapeutic approaches designed to reduce infarct size has become a major challenge for clinicians. The ischaemic injury is liable to extension as well as reduction in the reversible period dependent on various interacting haemodynamic and metabolic factors that will modify the effect of interventions. For instance decrease in myocardial oxygen requirement obtained by reduction of afterload might also result in reduction of coronary perfusion pressure and increase in heart rate. The resultant effect on the ischaemic area could therefore be unpredictable. Method for quantitating infarct size is consequently indispensable in the treatment of patients with acute ischaemic insult of the myocardium. Current techniques in use for assessing the ischaemic injury include:

- 1) grading of the ischaemic pain (3)
- 2) analysis of cumulated creatine kinase (CK) time-activity curves (4, 5)
- 3) adenosine imaging (6)

- 4) anaerobic metabolites in coronary sinus (7)
- 5) precordial ST-segment mapping (8)
- 6) precordial QR-mapping (9)

The use of the electrocardiogram for infarct sizing has obvious advantages: it is direct, simple, inexpensive, and non-invasive.

## Animal experiments ST-segment elevation

The relation between ST-segment elevation and coronary occlusion was probably first recognized in 1920 (10). Later Raab (11) demonstrated that epicardial ST-segment changes during coronary constriction were augmented by catecholamine stimulation of the myocardium. Experiments initiated in San Diego by Maroko et al. (1) showed that epicardial mapping of ST-segment changes was quite useful for indexing acute ischaemic injury of the myocardium underlying the exploring electrode (Fig. 1). Within 30 seconds after coronary artery occlusion, ST-segment elevation appears in the area of ischaemia indicated by cyanosis and systolic bulging. Areas outside the ischaemic zone do not show ST-segment elevation. Accordingly the size of the acute ischaemic region can be outlined by the number of epicardial positions displaying elevation. The extent of the elevation was taken to indicate the magnitude of ischaemic injury and the

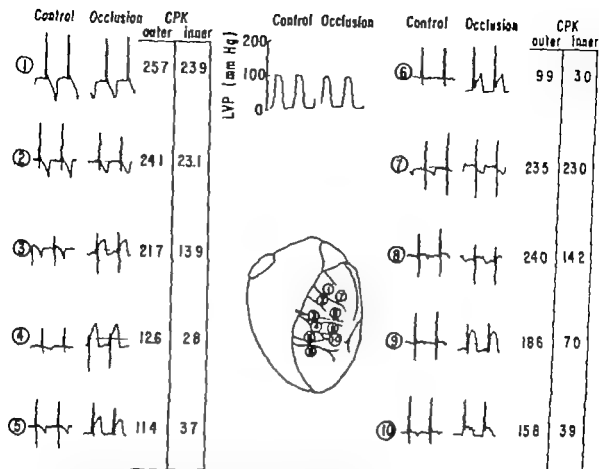


Fig 1 Mapping of epicardial ST-segment changes before and 15 min after coronary occlusion and creatine kinase (CK) activity 24 h later in corresponding subepicardial and subendocardial samples from a representative dog heart. LVP = left ventricular pressure. Locations of numbered sample sites and the occlusive coronary tie are indicated on the central diagram.

number of locations with ST-segment elevation to indicate the extent of the ischaemic area. The ischaemic changes in the ECG was transitory when the coronary occlusion was released within 20 minutes. Although the ST-segment changes in each position varied with time they were highly reproducible during repeated occlusions (1). The mapping of epicardial ST-segment elevations therefore provided a tool to study the effects on the ischaemic injury potentials of interventions applied between two subsequent occlusions of 15 minutes duration.

Several lines of evidence have been provided in support of the use of ST-segment elevation as a semi-quantitative index of myocardial ischaemic injury. ST-segment

elevations recorded by intramyocardial electrodes were closely related to reductions in intramyocardial oxygen tension (12). The magnitude of early elevation of epicardial ST segment in any given position correlated closely to the metabolic changes in the subjacent myocardium, as evidenced by lactate accumulation and by depletion of ATP and CK (13). ST-segment elevation also corresponded to regional accumulation of hydrogen ions and increase in  $\text{CO}_2$  tension (12). Moreover the magnitude of early elevations of ST-segments in any given epicardial position prefigured the ultimate extent of necrosis indicated by the depression of myocardial CK activity and by morphological evidence of cell death in subjacent

myocardial biopsies taken 24 hours after the coronary occlusion (Fig. 1) (14 15 16)

However there are limitations to the use of ST-segment changes as a quantitative index of myocardial injury. Although ST segment elevation was closely related to the myocardial injury as measured by regional CK depletion, the magnitude of epicardial ST-segment elevation was inversely related to the distance from the exploring electrode to the local injury. ST-segment elevation often did not occur when the myocardial injury was limited to subendocardial regions (15) (Fig. 2). A close relation was observed between ST-segment changes 15 minutes post occlusion and regional blood flow to the sub-epicardial region of the sampling site determined 24 hours later during microsphere injection (15). There was less ST-segment elevation for reductions in subendocardial blood

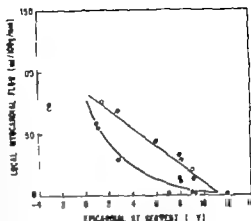


Fig. 3. Relation between epicardial ST-segments 15 min after coronary artery occlusion and regional blood flow in corresponding subepicardial (O) and subendocardial (●) regions 24 h later. The curves represent best fits obtained by least squares method. Regional flow was obtained by labelled microsphere technique.

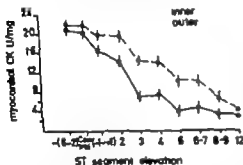


Fig. 2. Epicardial ST-segment changes and CK activity in homogenates from outer (O) and inner (●) regions of left ventricle. Epicardial ST-segment changes were recorded 15 min after coronary artery ligation from non-ischaemic and ischaemic areas. Whole wall biopsies from similar sites were taken 24 h later and divided into outer (subepicardial) and inner (subendocardial) portions.

flow fitting a non-linear relation (Fig. 3). This might explain why a less obvious relation was obtained in other studies that used microsphere determination of flow in the immediate post-occlusive period (17 18).

Regional flow in the ischaemic area is highly scattered, and unless small biopsies are taken, spurious results could be obtained. Lek et al. (19) applied intramyocardial platinum electrodes for ST-segment analysis and local flow determinations with hydrogen saturations and compared local intra-myocardial ST-elevation to local flow. Diminutions in flow were found to exceed 30–40% before ST-segment changes were observed, but were correlated closely with further reduction in flow. ST-segment elevation is therefore related to reduction in myocardial ischaemia, but epicardial ST-segment changes are less sensitive than those recorded from intramyocardial wires.

The ischaemia causes a reduction in the resting membrane potential and a shortening of the action potential. Thus an instantaneous potential difference is set up across the border between normal and abnormal polarized cells causing a current flow loop as the cell remains electrically coupled. Because shifts are caused simultaneously in resting and active membrane potential, changes



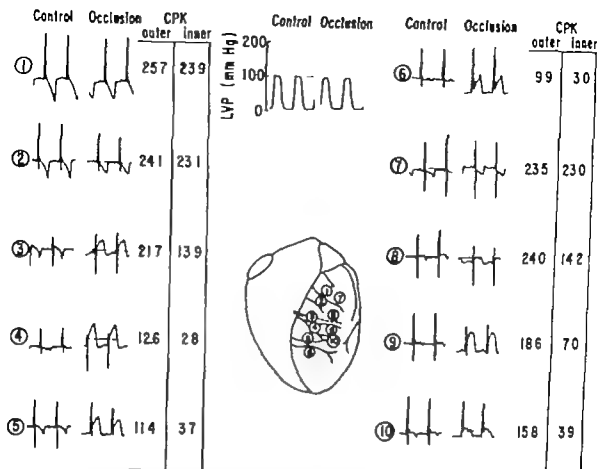


Fig 1 Mapping of epicardial ST segment changes before and 15 min after coronary occlusion and creatine kinase (CK) activity 24 h later in corresponding subepicardial and subendocardial samples from a representative dog heart. LVP = left ventricular pressure. Locations of numbered sample sites and the occlusive coronary tie are indicated on the central diagram.

number of locations with ST-segment elevation, to indicate the extent of the ischaemic area. The ischaemic changes in the ECG was transitory when the coronary occlusion was released within 20 minutes. Although the ST-segment changes in each position varied with time, they were highly reproducible during repeated occlusions (1). The mapping of epicardial ST-segment elevations therefore provided a tool to study the effects on the ischaemic injury potentials of interventions applied between two subsequent occlusions of 15 minutes duration.

Several lines of evidence have been provided in support of the use of ST-segment elevation as a semi-quantitative index of myocardial ischaemic injury. ST-segment

elevations recorded by intramyocardial electrodes were closely related to reductions in intramyocardial oxygen tension (12). The magnitude of early elevation of epicardial ST segment in any given position correlated closely to the metabolic changes in the subjacent myocardium, as evidenced by lactate accumulation and by depletion of ATP and CK (13). ST segment elevation also corresponded to regional accumulation of hydrogen ions and increase in  $\text{CO}_2$  tension (12). Moreover the magnitude of early elevations of ST-segments in any given epicardial position presaged the ultimate extent of necrosis indicated by the depression of myocardial CK activity and by morphological evidence of cell death in subjacent

myocardial biopsies taken 24 hours after the coronary occlusion (Fig. 1) (14 15 16).

However there are limitations to the use of ST-segment changes as quantitative index of myocardial injury. Although ST segment elevation was closely related to the myocardial injury as measured by regional CK depletion, the magnitude of epicardial ST-segment elevation was inversely related to the distance from the exploring electrode to the local injury. ST-segment elevation often did not occur when the myocardial injury was limited to subendocardial regions (15) (Fig. 2). A close relation was observed between ST-segment changes 15 minutes post occlusion and regional blood flow to the sub-epicardial region of the sampling site determined 24 hours later during microsphere injection (15). There was less ST-segment elevation for reductions in subendocardial blood

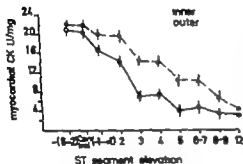


Fig 2 Epicardial ST-segments changes and CK activity in homogenates from outer (O) and inner (I) regions of ventricle. Epicardial ST segments changes were recorded 15 min after coronary artery ligation from non-ischaemic and ischaemic areas. Whole wall biopsies from similar sites were taken 24 h later and divided into outer (subepicardial) and inner (subendocardial) portions.

flow fitting non-linear relation (Fig. 3). This might explain why less obvious relation was obtained in other studies that used microsphere determination of flow in the immediate post-occlusive period (17 18).

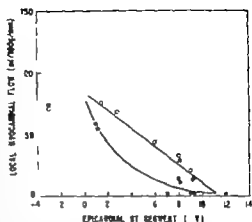


Fig 3 Relation between epicardial ST-segments 15 min after coronary artery occlusion and regional blood flow in corresponding subepicardial (O) and subendocardial (I) regions 24 h later. The curves represent best fits obtained by least squares method. Regional flow was obtained by labelled microsphere technique.

Regional flow in the ischaemic area is highly scattered, and unless small biopsies are taken, spurious results could be obtained. Lefven et al. (19) applied intramyocardial platinum electrodes for ST-segment analysis and local flow determinations with hydrogen desaturations and compared local intramyocardial ST-elevation to local flow. Diminutions in flow were found to exceed 30–40% before ST-segment changes were observed, but were correlated closely with further reduction in flow. ST-segment elevation is therefore related to reduction in myocardial ischaemia, but epicardial ST-segment changes are less sensitive than those recorded from intramyocardial sites.

The ischaemia causes reduction in the resting membrane potential and shortening of the action potential. Thus an instantaneous potential difference is set up across the border between normal and abnormal polarized cells causing a current flow as long as the cells remain electrically coupled. Because shifts are caused simultaneously in resting and active membrane potential, changes

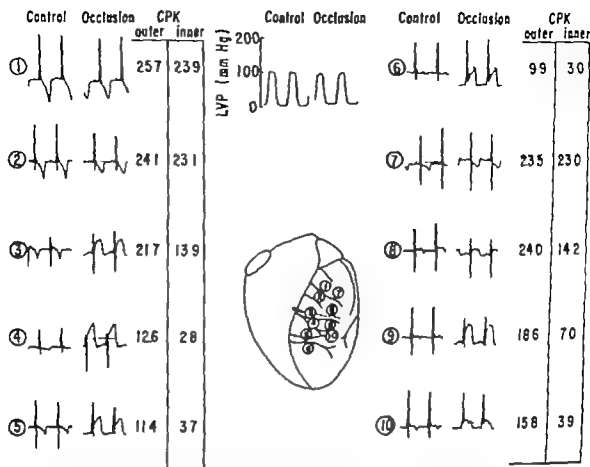


Fig 1 Mapping of epicardial ST-segment changes before and 15 min after coronary occlusion and creatine kinase (CK) activity 24 h later in corresponding subepicardial and subendocardial samples from a representative dog heart. LVP = left ventricular pressure. Locations of numbered sample sites and the occlusive coronary tie are indicated on the central diagram.

number of locations with ST-segment elevation to indicate the extent of the ischaemic area. The ischaemic changes in the ECG was transitory when the coronary occlusion was released within 20 minutes. Although the ST-segment changes in each position varied with time, they were highly reproducible during repeated occlusions (1). The mapping of epicardial ST-segment elevations therefore provided a tool to study the effects on the ischaemic injury potentials of interventions applied between two subsequent occlusions of 15 minutes duration.

Several lines of evidence have been provided in support of the use of ST segment elevation as a semi-quantitative index of myocardial ischaemic injury. ST-segment

elevations recorded by intramyocardial electrodes were closely related to reductions in intramyocardial oxygen tension (12). The magnitude of early elevation of epicardial ST-segment in any given position correlated closely to the metabolic changes in the subjacent myocardium as evidenced by lactate accumulation and by depletion of ATP and CK (13). ST segment elevation also corresponded to regional accumulation of hydrogen ions and increase in  $\text{CO}_2$  tension (12). Moreover the magnitude of early elevations of ST-segments in any given epicardial position presaged the ultimate extent of necrosis indicated by the depression of myocardial CK activity and by morphological evidence of cell death in subjacent

only ST-segment elevation in the first 15 minutes after coronary occlusion should be used for quantitative evaluation.

When due respect is given to the limits of the method, the close relation between early ST-segment elevation and ultimate extent of regional cell death, strongly qualifies the use of ST-segment elevation for indexing the ischaemic injury. The effect of interventions can therefore be studied by relating the ST-segment elevation obtained

15 minutes after coronary occlusion, before any intervention to the extent of necrosis 24 hours later as reflected in subjacent myocardial CK depression (1 14 15 16). The effect of intervention is evaluated by comparing treated and non-treated groups (Fig 4).

Thus, epicardial ST-segment mapping has proved to be a reliable index of myocardial ischaemia and has been extensively used to test interventions that might reduce or increase the ischaemic injury (1 14 16, 24).

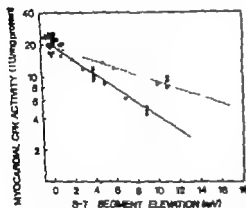


Fig 4 Depression of myocardial CK activity (per administration of  $\beta$ -pyridyl-carbonyl in animals with coronary artery occlusion. Epicardial recordings were obtained 15 min after coronary artery occlusion from anatomically identifiable sites. The artery was then released and permanently ligated. CK activity expressed on logarithmic scale was measured in homogenates from full-wall specimens obtained from the same sites 24 h later. Data from animals receiving  $\beta$ -pyridyl-carbonyl for 24 h (open circles) and from five untreated animals (closed circles). Solid line: regression line for control study (log CK =  $1.300 - 0.067$  ST =  $0.89$ ). Dotted line: regression line relating ST-segment elevation to per coronary artery occlusion before administration of  $\beta$ -pyridyl-carbonyl and log CK from corresponding sites 24 h later (log CK =  $1.278 - 0.033$  ST =  $0.78$ ). Animals receiving  $\beta$ -pyridyl-carbonyl showed less depression of myocardial CK activity than would have been expected from ST-segment elevation occurring before drug administration ( $P < 0.005$ ).

### ST-segment depression

Epicardial ST-segment depression is inconsistently observed at the outer margin of an ischaemic area. In areas with ST-segment depression, the resting and action membrane potentials are increased in contrast to opposite findings in regions with ST-segment elevation.

In most instances, it appears that epicardial ST-segment depression is a primary effect due to the hyperpolarization of the myocardial cell membrane (25) rather than a reciprocal effect of ST-segment elevation in the subendocardial regions, as previously suggested.

ST-segment depression is not associated with evolution of necrosis in any regions of the wall, and subjacent myocardial blood flow is not decreased (15) (Fig. 2 and 3). It follows that during acute coronary occlusion epicardial ST-segment depression has no prognostic significance on the evolution of necrosis.

### QRS-changes

Transformation of the ischaemic myocardial cell into an irreversibly damaged cell is reflected in reduction of the height of ST segment elevation. The point of no-return, however, is associated with conformational changes in the QRS complex appearing 30–45 minutes after the onset of ischaemia. These changes are reflected in the development of Q waves and the reduction of R waves in the immediate overlying epicardium (9). Similar changes are produced in-

will appear in both TQ- and ST-segments (20)

Currently used electrocardiographs are equipped with base-line compensation and do not discriminate between TQ depression and ST-elevation. The recorded ST-segment elevation is actually the sum of the two events (20). Interventions that alter either two will therefore interfere with the recorded ST segment elevation. The ischaemic injury however is always accompanied by true ST-segment elevation and by TQ segment depression, the latter probably being more important (21). But spurious results can be anticipated if an intervention affects selective ST or TQ segment shifts unrelated to the ischaemia.

The changes in resting and active membrane potential and consequently TQ-ST segment shifts are closely related to changes in ion transport and concentration gradients across the myocardial cell membrane. An ionic pump secures intracellular concentrations low in sodium and high in potassium. During ischaemia, the transmembraneous ion gradient is rapidly reduced, because the ionic pump is oxygen dependent and because accumulated potassium is not washed away. Regional coronary arterial perfusion with solution of high potassium concentration mimic local ST-segment elevation in the perfused area (22). Conversely washout of extracellular potassium in the ischaemic area reduces ST segment elevation. Spurious changes in the TQ-ST shift might occur with interventions which interfere with the ionic pump such as digitalis, quinidine, and by sympathetic stimulation. Regional differences in intramyocardial conduction velocity induced by the ischaemia, temperature changes, or acute myocardial dilation are also known to cause ST-segment shifts. Injury potential can be caused simply by applying pressure to the epicardial electrode. A cotton wick electrode soaked in saline is therefore preferable to solid electrodes

Analysis of ST-segment elevation for quantitative estimation of ischaemic injury is

an empirical method. Recently serious criticism has arisen mainly because it was found that ST-segment elevation in the centre of a large infarct occasionally disappeared as the area of infarction increased. The paradoxical reduction in ST-segment elevation in the centre of a large infarct has been theoretically explained based on the solid angle theorem (21). However the phenomenon is only observed in very large infarcts and is readily explained by intramyocardial conduction defects reflected in increased QRS duration. The epicardial ST-segment analysis therefore is applicable only when QRS is less than 0.06 seconds in dogs and less than 0.10 seconds in man. The time-point for reading of the ST segment elevation is crucial and should be standardized. Most authors have suggested 20 or 40 msec after end of the QRS complex. Whether the TP or PQ interval is the appropriate baseline is debatable. One or the other should be used (21).

The importance of temporal ST-segment changes during prolonged coronary occlusion to prognosticate evolution of myocardial necrosis has not been clearly defined. A rapid transition of the myocardial damage into irreversible injury might start as early as 20–30 minutes after coronary occlusion, depending on the amount of residual flow. Without intervention, epicardial ST-segment elevation decreases in the first few hours during uncomplicated myocardial infarction, but there is no intelligible relation between the decline in ST segment elevation and the evolution of necrosis. However ST-segment elevation reappears during interventions designed to increase infarct size conversely an abrupt reduction might be observed when coronary re-perfusion is started within 6 hours after occlusion (23–24). The ischaemic area might undergo necrosis and yet ST segment elevation can persist, as seen in large transmural infarction. The quantitative interpretation of ischaemic ST-segment elevation therefore becomes obscured when the myocardium undergoes necrosis. Although directional changes in ST-segment elevation follow interventions in the experimental model

tion of precordial ST-segment elevation has appeared useful for determining infarct extension (35-36), its usefulness for detecting the influence of drugs on the ischaemic injury is debatable. Pelides et al. (37) observed a marked reduction in precordial multipoint recording of ST-segment elevations when  $\beta$ -receptor blockade was induced as late as 72 hours after the onset of symptoms. Similar reductions were also obtained in patients with ST-segment elevation persisting as long as 9 days after the onset of infarction when there was no enzymatic evidence of necrosis (34). Because ischaemic ST-segment elevation signals more than 50 % reduction in myocardial flow relative to myocardial oxygen requirement, inevitably leading to rapid necrosis, it is difficult to reconcile the persisting ST-segment elevation should reflect reversible ischaemic injury long after necrosis has ended. The alidity of reduction of ST-segment height due to intervention later than 6 hours after onset of symptoms should therefore be considered with care and more than 50 % reduction of ST-segment elevation should be required. Within these limits reduction of ST-segment elevation has been observed with drugs such as hyaluronidase (38) nitroglycerine (39) and  $\beta$ -pyridylcarbinol (40) and also with inhalation of 40 % oxygen (41).

### QRS-changes

Appearance of Q waves correlate well with electrocardiographic abnormalities (42), specifically the extent of dyssynergia, and inversely with ejection fractions (43). Post-mortem studies has shown good correlation between QR amplitude changes in conventional 12 leads ECG and the actual anatomical extent of anterior infarcts, but poorer correlation to posterior infarcts (44). Recently Hultis et al (9) suggested that precordial mapping of early ST-segment elevation and later development of QR changes should be combined to assess the effects of interventions on a myocardial infarct size. By determining how many sites with initial

evidence of ischaemia (ST-segment elevation) progress to evidence of necrosis (QR amplitude changes) the effect of intervention can be evaluated in groups of patients.

QR amplitude changes will only grossly reflect the conformational changes which take place in the whole spatial QRS complex due to necrosis. Furthermore, posterior infarcts and infarcts in the right ventricle are not readily reflected in precordial QR amplitude changes. More recently therefore we suggested the use of orthogonal vector loops for determining the evolution of an infarction (40). The mean spatial QRS vector is calculated sequentially during the evolution of necrosis, and by vectorial subtraction, a temporal infarct vector can be obtained. The evolution of the infarct vector in uncomplicated infarcts progresses exponentially parallel to but preceding the accumulated CK curve by 2-3 hours (Fig. 5).

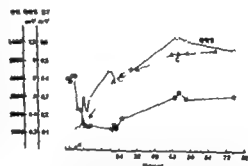


Fig. 5 Temporal changes in the QRS infarct vector accumulated CK and ST-segment vector in patient with acute myocardial infarction. The partial QRS and ST vectors were obtained from an orthogonal lead system (Frank) and the infarct vector was derived by vectorial subtraction of subsequent QRS vector recordings.

Interventions aimed at reducing infarct size have been shown to halt the evolution of the QRS infarct vector (Fig. 6). The use of QRS vector loop analysis has the advantage that any change in the QRS complex contributes to the spatial infarct vector. Consequently the precision is increased and

mediately when a defined necrosis is abruptly caused by myocardial formalin injection and remain constant during subsequent hours (26).

QRS changes are closely related to the irreversible loss of tissue due to abolition of membrane action potential in subjacent myocardial tissue. Local injury potential can no longer be elicited by applying pressure to the epicardial electrode (27). In ischaemic myocardium, the QR changes in epicardial leads evolve with time. The ultimate QRS complexes in epicardial sites are correlated with the subjacent extent of necrosis, measured histochemically and histologically (9). When the ratio between the increase in Q wave and reduction in R wave is used, an index is obtained which is closely related to the extent of subjacent myocardial necrosis and also to the 15 minutes ST-segment elevation in the same position (9). The amplitude changes of Q and R waves were used to evaluate interventions aimed at reducing infarct size in dogs. The height of early ST-segment elevation in epicardial sites was quantitatively related to later development of QRS amplitude changes. Consequently the effect of interventions can be studied with respect to the progression of QR changes relative to the initial ST-segment elevation.

## Studies in human

### ST-segment elevation

Precordial ST segment mapping has been applied in patients to delineate changes in myocardial ischaemia (8, 28). Animal experiments have demonstrated that the extent and magnitude of ST segment elevations in 35 precordial leads correlated quantitatively with ST segment elevations in epicardial leads during coronary occlusion and varied appropriately with interventions (8, 29). The technique, however, applies only to patients with anterior wall infarction, because of the relative insensitivity of diaphragmatic located infarcts in the conventional 12 lead electrocardiogram (8).

Precordial mapping of ST-segment height can only be used to assess directional

changes in the ischaemic injury. As many as 72 precordial electrodes have been used. The large number of leads offer little advantage in sensitivity compared with the use of selected electrode positions displaying the largest ST-segment elevation. Because recording and measurements of multiple electrocardiograms are timeconsuming and awkward to the patients, selected electrode positions have been preferred. Recently continuous recording of average ST elevation from 35 precordial leads were obtained by computer analysis (30).

Akiyama et al. (31) suggested the use of an orthogonal lead system. Instead of averaging ST-segment elevation in multiple precordial electrodes, vectorcardiography permits the calculation of one spatial ST-segment vector. Good correlation was found between a precordial map of ST-segment elevation and the spatial ST-segment vector. The study also suggested that inferior wall myocardial infarction can be evaluated by vector analysis. Epicardial electrocardiographic recordings of an infarct depends critically on the distance and orientation of the recording electrodes relative to the infarct, body build, skin resistance, and accompanying pericarditis. ST segment mapping is therefore limited to be used when the patient serves as his own control; it is not valid for comparisons among different patients (8, 32). A significant but weak correlation has been found between ST-segment elevation within the first hour after onset of symptoms and the ultimate infarct size evaluated by creatinephosphokinase (MB-CK) isoenzyme but no correlation was found when ST-segments were obtained more than one hour after the onset of symptoms (33).

The ST-segment elevation decreases slowly to normal values in uncomplicated myocardial infarction, but can remain elevated long after myocardial enzyme release has ended (34). ST-segment elevation remains high in patients with extensive transmural myocardial infarction and congestive heart failure and major increase in the ST-segment strongly suggests a fatal outcome or reinfarction (35). Although the determina-

9. Hillis, L. D. Askenazi, J. Braunwald, E., Radvany F. Muller J. E., Fishbein, M. C. and Maroko, P. R.: Use of changes in the epicardial QRS complex to assess interventions which modify the extent of myocardial necrosis following coronary artery occlusion. *Circulation* 54 591 1976
10. Pardee, H. E. B. An electrocardiographic sign of coronary artery obstruction. *Arch. Int. Med.* 26 244 1920
11. Raab, W. Van Lath, P. Lepeschkin, E. and Herrlich, H. C. Catecholamine induced myocardial hypoxia in the presence of impaired coronary dilatability independent of external cardiac work. *Am. J. Cardiol.* 10 455 1962
12. Khuri, S. F. Fisherry J. T. O'Riordan, J. B., Pitt, B. Brawley R. K., Donaboo, J. S. and Goet, V. L. Changes in intramyocardial ST segment voltage and gas tensions with regional myocardial ischemia in the dog. *Circ. Res.* 37 455 1975
13. Karlsson, J. Templeton, G. K. and Willerson, J. T. Relationship between epicardial ST segment changes and metabolism during acute coronary insufficiency. *Circ. Res.* 32 725 1973
14. Kjekshus, J. K. and Myer, O. D. Effect of inhibition of lipolysis on infarct size after experimental coronary artery occlusion. *J. Clin. Invest.* 52 1578 1973
15. Kjekshus, J. K., Maroko, P. R. and Sobel, B. E. Distribution of myocardial injury and its relation to epicardial ST-segment changes after coronary artery occlusion in the dog. *Cardiovasc. Res.* 6 490, 1972
16. Maroko, P. R., Libby P. Bloor, C. M., Sobel, B. E. and Braunwald, E. Reduction by hyaluronidase of myocardial necrosis following coronary artery occlusion. *Circulation* 46: 430, 1972
17. Smith, H. J. Singh, B. N. Norris, R. M., Murray J. B. and Hurley P. J.: Changes in myocardial blood flow and ST-segment elevation following coronary artery occlusion in dogs. *Circ. Res.* 36 697 1975
18. Irvin, R. G. and Cobb, F. R.: Relationship between epicardial ST segment elevation, regional myocardial blood flow and extent of myocardial infarction in awake dogs. *Circulation* 55 825 1977
19. Lekven, J. Hebekk, A., Fønsterlien, E. and Kili, P.: Relationship between ST-segment elevation and local tissue flow during myocardial ischemia in dogs. *Cardiovasc. Res.* 9 627 1975
20. Samson, W. E. and Scher A. M.: Mechanism of ST-segment alterations during acute myocardial injury. *Circ. Res.* 8: 760, 1960
21. Holland, R. P. and Brooks, H. Precordial and epicardial surface potentials during myocardial ischemia I: the pig. A theoretical and experimental analysis of the TQ and ST-segment. *Circ. Res.* 37 471 1975
22. Pruzmetel, M., Ekmekci, A., Toyoshima, H. and Kwocynski, J. K.: Angina pectoris III Demonstration of a chemical origin of ST-deviation. *Am. J. Cardiol.* 3 276, 1959
23. Capone, R. J. Moss, A. S. and Sydlík, P. A.: Precordial ST-segment mapping. A sensitive technique for the evaluation of myocardial injury. *Chem. Abstr.* 577 1975
24. Maroko, P. R., Libby P. Ginks, W. R., Bloor C. M., Shell W. E., Sobel, B. E. and Ross, J. Coronary artery reperfusion. I. Early effects on local myocardial function and the extent of myocardial necrosis. *J. Clin. Invest.* 51 2710, 1972



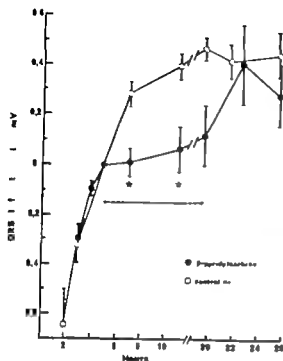


Fig 6 The effect of inhibition of lipolysis on the evolution of the spatial QRS infarct vector in patients (40). After more than one hour observation period the patients were randomized to either treatment with  $\beta$ -pyridyl-carbinol or no treatment (control).

its use is also extended to posterior and right ventricular infarcts. Sequential evaluation of QRS changes might have potential value in reflecting the extent and rate of necrosis development, but its practical use still awaits further trials.

Despite its shortcomings, the electrocardiographic technique offers an instant and simple way to monitor infarct evolution. As yet, no other method is available that can effectively presage at the bedside the effect of the myocardial insult.

## References

- 1 Maroko, P R., Aekshus, J K., Sobel B E., Watanabe, T., Covell J W, Ross, J and Braunwald, E. Factors influencing infarct size following experimental coronary artery occlusions. *Circulation* 43: 67 1971

- 2 Page, D L., Canfield, J B., Kistor J A., De Sanctis, R. W and Sanders, C. A.: Myocardial changes associated with cardiogenic shock. *N Engl. J Med.* 285: 133 1971
- 3 Waagstein, F and Hjalmarson, A. F Double — blind study of the effect of cardioselective beta blockade on chest pain in acute myocardial infarction. *Acta Medica Scand. Suppl.* 587: 201 1975
- 4 Shell W E., Aekshus, J K. and Sobel, B E. Quantitative assessment of the extent of myocardial infarction in the conscious dog by means of analysis of serial changes in serum creatine phosphokinase activity. *J Clin Invest.* 50: 2614 1971
- 5 Shell, W E., Lavelle, J F., Covell J W and Sobel, B E. Early estimation of myocardial damage in conscious dogs and patients with evolving acute myocardial infarction. *J Clin. Invest.* 52: 2579 1973
- 6 Pohost, G M., Zir L. M. Moore, R. H., Mc Kusick, K. A., Guiney T E. and Beller G A.: Differentiation of transiently ischemic from infarcted myocardium by serially imaging after a single dose of Thallium 201. *Circulation* 55: 294 1977
- 7 Remme W J., Jong, J W and Verdoorn P D. Effects of pacing — induced ischemia on hypoxanthine efflux from the human heart. *Am. J Cardiol* 40: 55 1977
- 8 Maroko, P R., Libby P, Covell, J W, Sobel, B E., Ross, J Jr and Braunwald E.: Precordial S-T segment elevation mapping: An atraumatic method for assessing alterations in the extent of myocardial ischemic injury. *Am. J Cardiol.* 29: 223 1972

- 9 Hillis, L. D. Askenazi, J. Braunwald, E., Radvany P. Muller J. E., Fishbein, M. C. and Maroko, P. R.: Use of changes in the epicardial QRS complex to assess interventions which modify the extent of myocardial necrosis following coronary artery occlusion. *Circulation* 54: 591 1976
10. Pardee, H. E. B.: An electrocardiographic sign of coronary artery obstruction. *Arch. Int. Med.* 6 244 1920
- 11 Raab, W. Van Lath, P. Lepeschka, E. and Herrlich, H. C. Catecholamine induced myocardial hypoxia in the presence of impaired coronary dilatability independent of external cardiac work. *Am. J. Cardiol.* 40 455 1962
12. Khuri, S. F. Flaherty J. T. O'Riordan, J. B., Pitt, B. Brawley R. K., Donahoo J. S. and Gots, V. L.: Changes in intramyocardial ST-segment voltage and gas tensions with regional myocardial ischemia in the dog. *Circ. Res.* 37 435 1975
- 13 Karlsson, J. Tenoplen, G. K. and Willerson, J. T. Relationship between epicardial ST segment changes and metabolism during acute coronary insufficiency. *Circ. Res.* 32 725 1973
- 14 Kytekin, J. K. and Myer, O. D. Effect of inhibition of lipolysis on infarct size after experimental coronary artery occlusion. *J. Clin. Invest.* 52 1578, 1973
- 15 Kytekin, J. K., Maroko, P. R. and Sobel, B. E. Distribution of myocardial injury and its relation to epicardial ST-segment changes after coronary artery occlusion in the dog. *Cardiovasc. Res.* 6 490, 1972
- 16 Maroko, P. R. Libby P. Moor C. M., Sobel, B. E. and Braunwald, E.: Reduction by hyaluronidase of myocardial necrosis following coronary artery occlusion. *Circulation* 46: 430, 1972
- 17 Smith, H. J. Singh, B. N. Norris, R. M., Murray J. B. and Harley P. J. Changes in myocardial blood flow and ST-segment elevation following coronary artery occlusion in dogs. *Circ. Res.* 36: 697 1975
- 18 Irvin, R. G. and Cobb, F. R. Relationship between epicardial ST segment elevation, regional myocardial blood flow and extent of myocardial infarction in awake dogs. *Circulation* 55: 825, 1977
- 19 Lekven, J. Hebekk, A., Fønsterhen, E. and Küll, F. Relationship between ST-segment elevation and local tissue flow during myocardial ischemia in dogs. *Cardiovasc. Res.* 9: 627 1975
20. Samson, W. E. and Scher A. M.: Mechanism of ST-segment alterations during acute myocardial injury. *Circ. Res.* 8 780, 1960
- 21 Holland, R. P. and Brooks, H. Precordial and epicardial surface potentials during myocardial ischemia in the pig. A theoretical and experimental analysis of the TQ and ST-segment. *Circ. Res.* 37 471 1975
22. Prinzmetal, M., Ekmekeci, A., Toyoshima, H. and Kwoczynski, J. K.: Angina pectoris III. Demonstration of chemical origin of ST-deviation. *Am.-J. Cardiol.* 3 276, 1959
- 23 Capone, R. J. Moss, A. S. and Sydlík, P. A. Precordial ST-segment mapping. A sensitive technique for the evaluation of myocardial injury. *Chest* 67 577 1975
- 24 Maroko, P. R., Libby P. Ginks, W. R., Moor C. M., Shell, W. E., Sobel, B. E. and Ross, J.: Coronary artery reperfusion. I. Early effects on local myocardial function and the extent of myocardial necrosis. *J. Clin. Invest.* 51 2710, 1972

- 25 Toyoshima, H., Ekmekeci, A., Flamm, E., Mizund, Y., Nagaya, T., Nakayama R., Yamada, K. and Prinzmetal, M. Angina pectoris VIII. The nature of ST-depression in acute myocardial ischemia.  
*Am. J. Cardiol.* 13 498, 1964
- 26 Abildskov J. A. and Boyle, R. S. Further studies of the electrocardiographic effects of experimental myocardial lesions.  
*Am. Heart J* 69 49 1965
- 27 Prinzmetal M., Kennamer R. and Maxwell M.: Studies on the mechanism of ventricular activity VIII The genesis of the coronary QS wave in through and-through infarction.  
*Am. J. Med.* 17 610, 1954
- 28 Pelides, L. J. Reid, D. S. Thomas, M. and Shillingford, J. P. Inhibition by  $\beta$  blockade of ST-segment elevation after acute myocardial infarction in man.  
*Cardiovasc. Res.* 6 295 1972
- 29 Muller J. E., Maroko P. R. and Braunwald, E.: Evaluation of precordial electrocardiographic mapping as a mean of assessing changes in myocardial injury  
*Circulation* 52 16, 1975
- 30 Luxton, M. R. Russel, D. C., Murray A., Williamson, D., Neilson, J. M. M. and Oliver M. F. Precordial ST-segment elevation. New technique for continuous recording and analysis.  
*Brit. Heart J* 39 493 1977
- 31 Akiyama, T. Hodges, M. Briddle, T. L., Zawrotay B. and Vangellow C. Measurement of ST-segment elevation in acute myocardial infarction in man. Comparison of a precordial mapping technique and the Frank vector system.  
*Am. J. Card.* 36 155 1975
- 32 Nilsen B. L.: ST-segment elevation in acute myocardial infarction. Prognostic importance.  
*Circulation* 48 338 1973
- 33 Selwyn, A. P., Ogunro, E. A. and Shillingford, J. P. Natural history and evaluation of ST segment changes and MB CK release in acute myocardial infarction.  
*Brit. Heart J* 39 988 1977
- 34 Norris, R. M., Baratt Boyes, C., Heng M. K. and Singh, H. N. Failure of ST-segment elevation to predict severity of acute myocardial infarction.  
*Brit. Heart J* 38 85 1976
- 35 Kronenberg, M. W., Hodges, M., Akiyama, T. Roberts, D. L., Ehrlich, D. A., Biddle, T. L. and Yu, P. N.: ST-segment variations after acute myocardial infarction. Relationship to clinical status.  
*Circulation* 54 756, 1976
- 36 Reid, P. R., Taylor D. R., Kelly D. T., Weisfeldt, M. L., Humphries, J. O. Ross, R. S. and Pitt, B. Myocardial infarct extension detected by precordial ST segment mapping.  
*N. Eng. J. Med.* 290 123 1974
- 37 Pelides, L. J. Reid, D. S., Thomas, M. and Shillingford J. P. Inhibition by  $\beta$ -blockade of the ST-segment elevation after acute myocardial infarction in man.  
*Cardiovasc. Res.* 6: 295 1972
- 38 Maroko, P. R., Davidson D. M., Libby P., Hagan, A. D. and Braunwald, E. Effects of hyaluronidase administration on myocardial ischemic injury in acute infarction.  
*Ann Intern. Med.* 82 516, 1973
- 39 Come, P. C., Flaherty J. T. Baurd, M. G. Rooleau, J. R., Weisfeldt, M. L., Greene, H. L., Becker L. and Pitt, B. Reversal by phenylephrine of the beneficial effects of intravenous nitroglycerin in patients with acute myocardial infarction  
*N. Eng. J. Med.* 293 1003 1975
- 40 Hekshus, J. K. and Grottrum, P. Modification of acute myocardial in

infarction by intravenous 8-pyridylcarbamol.

Proceedings of a conference on Acute and Long Term Medical Management of Myocardial Ischaemia, Copenhagen 8-9 September 1977. Ed. Å Hjalmarson and L. Wilhelmsen.

Möndal 1978, p. 373

41. Madias, J. E., Madias, N. E., Hood, W. B.:

Precordial ST-segment mapping. 2. Effects of oxygen inhalation on ischemic injury in patients with acute myocardial infarction.

Circulation 53: 411 1976

42. Gottlieb, R. S., Duce, P. R., Kasparian, H., Scariato, A. and Bress, A. N. Correlation of abnormal Q waves, co-

ronary pathology and ventricular contractility

Am. Heart J 90: 451 1975

43. Awan, N. A., Miller, R. R., Vera, Z., Janzen, D. A., Amsterdam, E. A. and Mason, D. T.:

Non invasive assessment of cardiac function and ventricular dyssynergy by precordial Q wave mapping in anterior myocardial infarction.

Circulation 55: 833, 1977

44. Savage, R. M., Wagner, G. S., Ideker, R. E., Podolsky, S. A. and Hackel, D. B.

Correlation of postmortem anatomic findings with electrocardiographic changes in patients with myocardial infarction.

Circulation 55: 279 1977

- 25 Toyoshima, H., Ekmekeci, A., Flamm, E., Mizund, Y., Nagaya, T., Nakayama R., Yamada, K. and Prinzmetal, M. Angina pectoris. VIII The nature of ST-depression in acute myocardial ischemia.  
*Am J Cardiol* 13 498 1964
- 26 Abildskov J. A. and Boyle, R. S.: Further studies of the electrocardiographic effects of experimental myocardial lesions.  
*Am. Heart J* 69 49 1965
- 27 Prinzmetal M., Kennamer R. and Maxwell, M. Studies on the mechanism of ventricular activity VIII The genesis of the coronary QS wave in through and through infarction.  
*Am J Med* 17 610 1954
- 28 Pelides, L. J., Reid D. S. Thomas, M. and Shillingford, J. P. Inhibition by  $\beta$ -blockade of ST-segment elevation after acute myocardial infarction in man  
*Cardiovasc. Res.* 6 295 1972
- 29 Muller J. E. Maroko P. R. and Braunwald, E. Evaluation of precordial electrocardiographic mapping as a mean of assessing changes in myocardial injury  
*Circulation* 52 16, 1975
- 30 Luxton M. R. Russel, D. C. Murray A. Williamson, D. Neilson, J. M. M. and Oliver M. F. Precordial ST-segment elevation. New technique for continuous recording and analysis.  
*Brit. Heart J* 39 493 1977
- 31 Akiyama, T. Hodges, M., Briddle, T. L., Zawrotay II and Vangellow C. Measurement of ST-segment elevation in acute myocardial infarction in man. Comparison of a precordial mapping technique and the Frank vector system.  
*Am. J Card.* 36 155 1975
- 32 Nilsen, B. L. ST-segment elevation in acute myocardial infarction. Prognostic importance.  
*Circulation* 48: 338 1973
- 33 Selwyn, A. P., Ogunro, E. A. and Shillingford, J. P. Natural history and evaluation of ST segment changes and MB Ch release in acute myocardial infarction.  
*Brit. Heart J* 39: 988 1977
- 34 Norris, R. M., Baratt Boyes, C., Heng, M. K. and Singh, B. N. Failure of ST-segment elevation in predict severity of acute myocardial infarction.  
*Brit. Heart J* 38 85 1976
- 35 Kronenberg, M. W., Hodges, M., Akiyama, T., Roberts, D. L., Ehrlich, D. A., Biddle, T. L. and Yu, P. N. ST segment variations after acute myocardial infarction. Relationship to clinical status.  
*Circulation* 54: 756, 1976
- 36 Reid, P. R., Taylor D. R., Kelly D. T. Weisfeldt, M. L., Humphries, J. O. Ross, R. S. and Pitt, B. Myocardial infarct extension detected by precordial ST-segment mapping.  
*N Eng. J Med.* 290: 123 1974
- 37 Pelides, L. J. Reid, D. S., Thomas, M. and Shillingford, J. P. Inhibition by  $\beta$ -blockade of the ST-segment elevation after acute myocardial infarction in man.  
*Cardiovasc. Res.* 6 295 1972
- 38 Maroko, P. R. Davidson, D. M., Libby P., Hagan, A. D. and Braunwald, E. Effects of hyaluronidase administration on myocardial ischemic injury in acute infarction  
*Ann Intern. Med.* 82 516, 1975
- 39 Come, P. C., Flaherty J. T. Baird, M. G. Rouleau J. R. Weisfeldt, M. L., Greene, H. L., Becker L. and Pitt, B. Reversal by phenylephrine of the beneficial effects of intravenous nitroglycerin in patients with acute myocardial infarction  
*N Eng J Med.* 293 1003 1975
- 40 Hjekshus, J. K. and Grottrum, P.: Modification of acute myocardial in

## LD-isoenzymes

The five common LD isoenzymes are named in order of rapidity of migration toward the anode in an electrophoretic field. LD<sub>1</sub> is the fastest and LD<sub>4</sub> the slowest in conventional systems. Each isoenzyme is a tetrameric unit composed of four subunits of two possible types. The physical properties of individual isoenzymes are determined by the relative percentage of each type of subunit contained (44). Extracts of myocardium contain primarily LD<sub>1</sub> and small amounts of LD<sub>2</sub>, whereas those from liver or skeletal muscle contain mostly LD<sub>4</sub> and LD<sub>5</sub>. Separation of LD is generally performed by chemical fractionation techniques, such as heat stability (LD<sub>T</sub>), resistance to inhibition by urea (urea stabl LD), or affinity for alpha-hydroxybutyric acid as a substrate (αHBD). Several reports refer to the results of the different separation techniques (LD<sub>1</sub>, LD<sub>T</sub>, urea stabl LD, αHBD) as "heart" LD. But none of these fractions of LD are specific of myocardial necrosis. Elevation of "heart" LD activity has been reported after renal infarction (3) and in about 25 per cent of patients with myocardium (9). Furthermore, the rise of serum "heart" LD activity relatively late after AMI suggests that "heart" LD elevations might reflect, in part, the release of enzymes from nonmyocardial components, such as red cells or inflammatory cells participating in the reaction to infarction within the heart (65).

However the primary distal source in using elevated "heart" LD activity in the diagnosis of AMI is that red blood cells contain substantial amounts of "heart" LD thus minimum haemolysis in blood sample will elevate the activity of this isoenzyme (4).

None the less, the long half life of "heart" LD is an advantage in certain cases. In typical patient with AMI "heart" LD activity exceeds the normal range within about 12 hours from the onset of symptoms, reaches peak in 48–60 hours, and declines to the normal range within 8–10 days (64). This prolonged rise is of advantage in patients with a long delay between

onset of symptoms and admittance to hospital.

## CK-isoenzymes

CK is a dimeric molecule composed of two types of monomer: the M (muscle) and the B (brain) subunits (12). Combinations of these subunits result in the occurrence of the three isoenzymes of CK designated CK-MB, CK-BB, and the hybrid CK-MB. Electrophoretic separation of CK was first performed by Burger and associates (8) and was followed by others (15, 31, 61). These isoenzymes are found in differing proportions in various tissues, the CK-MB isoenzyme in large quantities in skeletal muscle and CK-BB mainly in nervous tissue. The myocardium contains both CK-MB and CK-MB, but there are divergent reports concerning the ratio between the two isoenzymes (13, 35, 36, 70, 73). However many authors have considered CK-MB as cardio-specific (22, 47, 59, 73) this statement is further discussed later in this review. Recently a mitochondria-specific form of CK has been reported in the guinea pig heart (53).

## Determination methods

A number of procedures have been reported for the separation and quantitation of the three isoenzymes. In general, these techniques involve an initial separation with the use of either electrophoresis (33, 59, 66) or ion exchange chromatography (28, 46) followed by either fluorometric or spectrophotometric quantitation. More recently immunological techniques (30, 80) and methods with specific activation of the CK-MB (55) have been reported. Generally lower activities of CK-MB have been reported with chromatographic techniques than with electrophoretic techniques. This finding was verified by Ogumuro and associates (54) who compared their agarose gel electrophoresis technique with an ion exchange procedure (46) and with the diethylenetriamine oxidase method described by Rao and associates (55). They found CK-MB activity with the electrophoretic techn-

# Enzymes in acute myocardial infarction Diagnosis with special reference to creatine kinase MB Isoenzyme

Rolf Nordlander

Dept of Medicine Karolinska Institute at Huddinge hospital  
HUDDINGE, SWEDEN

Elevated serum enzyme activity has become a cornerstone in the diagnosis of acute myocardial infarction (AMI). Diagnostic enzymology was first associated with the diagnosis of pancreatitis, 1908 (78). In 1954 Karmen, Wroblewski, La Due and their associates demonstrated that aspartatransferase (ASAT GOT) and lactic dehydrogenase (LD LDH) activity in serum increased after AMI (32). Creatine kinase (CK CPK) was first described by Lohmann (42) and introduced into clinical medicine by Ebashi and associates (18). Elevation of CK after AMI was first reported by Dreyfus and associates (17); several reports soon followed (20, 34, 68). Determinations of ASAT, LD and CK have since been widely used in the diagnosis of AMI.

The activity of other enzymes, such as aldolase, malic dehydrogenase, isomerase, and isocitric dehydrogenase (ICD) can also increase after AMI (75) but the clinical use is limited.

However, the three routine enzyme tests ASAT, LD and CK are not specific for the myocardium; higher concentrations of each of these enzymes might be present in other tissues.

Although ASAT activity increases in about 90 per cent of patients after AMI (21), elevated activity can also result from pulmonary embolism (11), myocarditis (51), pericarditis (75), tachycardia (60), hepatic congestion (74), primary hepatic or biliary

tract disease (6), skeletal muscle disorders (2), infections (14), oral contraceptive ingestion (40), after surgery (41), after cardiac catheterization (48) and after electroconversion (37). It is worthy of note that elevation of ASAT activity within the normal range has been reported also after intramuscular injections (38, 81).

By the same token, elevated LD activity is a sensitive but non-specific indicator of myocardial damage, detectable not only in about 90 per cent of patients with AMI (64) but also in those with congestive heart failure (6), pulmonary embolism (69), haemolysis and megaloblastic anaemia (72), hepatitis (79), neoplastic disease (72), myxedema (25) and skeletal muscle trauma (41).

Elevated CK activity is seen in virtually all patients sustaining AMI (21, 57); it can be seen with several diseases such as muscular dystrophy (18), pericarditis and myocarditis (29), paroxysmal tachycardia (27), pulmonary embolism (36), cerebrovascular diseases (1), myxedema (24), diabetic coma (76) and hypothermia (43). Elevated CK activity has also been reported after prolonged activity (26), after treatment with intramuscular injections (45), after surgery (16), after cardiac catheterization (48), after electroconversion (37) and after radiotherapy (49).

However, a higher specificity can be achieved by the use of LD and CK isoenzymes.

## LD-isoenzymes

The five common LD isoenzymes are named in order of rapidity of migration toward the anode in an electrophoretic field. LD<sub>1</sub> is the fastest and LD<sub>5</sub> the slowest in conventional systems. Each isoenzyme is tetrameric unit composed of four subunits of two possible types. The physical properties of individual isoenzymes are determined by the relative percentage of each type of subunit contained (44). Extracts of myocardium contain primarily LD<sub>1</sub> and small amounts of LD<sub>2</sub>, whereas those from liver or skeletal muscle contain mostly LD<sub>4</sub> and LD<sub>5</sub>. Separation of LD is generally performed by chemical fractionation techniques, such as heat stability (LD<sub>5</sub>), resistance to inhibition by urea (urea stable LD), or affinity for alpha hydroxybutyric acid as a substrate (aHBD). Several reports refer to the results of the different separation techniques (LD<sub>1</sub>, LD<sub>2</sub>, urea stable LD, aHBD) as "heart LD." But none of these fractions of LD are specific of myocardial necrosis. Elevation of "heart LD" activity has been reported after renal infarction (5) and in about 33 per cent of patients with myocarditis (9). Furthermore, the rise of serum "heart LD" activity relatively late after AMI suggests that "heart LD" elevations might reflect, in part, the release of isoenzymes from nonmyocardial components, such as red cells or inflammatory cells participating in the reaction to infarction within the heart (65).

However the primary disadvantage in using elevated "heart" LD activity in the diagnosis of AMI is that red blood cells contain substantial amounts of "heart LD" thus minimum haemolysis in blood sample will elevate the activity of this isoenzyme (4).

None the less, the long half life of "heart LD" is advantageous in certain cases. In a typical patient with AMI "heart" LD activity exceeds the normal range within about 12 hours from the onset of symptoms, reaches peak in 48-60 hours, and declines to the normal range within 8-10 days (64). This prolonged rise is of diagnostic value in patients with a long delay between

onset of symptoms and admittance to hospital.

## CK-isoenzymes

CK is a dimeric molecule composed of two types of monomers: the M (muscle) and the B (brain) subunits (12). Combinations of these subunits result in the occurrence of the three isoenzymes of CK designated CK-MM, CK-BB, and the hybrid CK-MB. Electrophoretic separation of CK was first performed by Burger and associates (8) and was followed by others (15, 31, 61). These isoenzymes are found in differing proportions in various tissues, the CK-MM isoenzyme in large quantities in skeletal muscle and CK-BB mainly in nervous tissue. The myocardium contains both CK-MM and CK-MB, but there are divergent reports concerning the ratio between the two isoenzymes (13, 33, 35, 56, 70, 73). However many authors have considered CK-MB as "cardiospecific" (22, 47, 59, 73); this statement is further discussed later in this review. Recently, mitochondrial-specific form of CK has been reported in the guinea pig heart (53).

## Determination methods

A number of procedures have been reported for the separation and quantitation of the three isoenzymes. In general, these techniques involve an initial separation with the use of either electrophoresis (33, 59, 66) or ion exchange chromatography (28, 46) followed by either fluorometric or spectrophotometric quantitation. More recently immunological techniques (30, 80) and methods with specific activation of the CK-MB (55) have been reported. Generally lower activities of CK-MB have been reported with chromatographic techniques than with electrophoretic techniques. This finding was verified by Ogumro and associates (34) who compared their agarose gel electrophoresis technique with an ion exchange procedure (46) and with the diethylenetriamine acetic acid method described by Rao and associates (55). They found CK-MB activity with the electrophoretic techni-



que to be twice as high as the other two techniques. Thus, it seems reasonable to explain much of the discrepancy in the literature concerning CK—MB activity by methodological differences.

Moreover most of the described methods

are technically complicated and time consuming and thus limits their clinical use. However recently a promising immunological technique using anti M antibodies has been presented (80) but it still needs further clinical evaluation.

Table 1

Human tissue CK—MB distribution according to three references.

Tissue	Ogunro et al, 1977		Roberts et al 1975		Jockers Wretou & Pfeleiderer 1975	
	Total Ch—(* activity	MB %	Total CK—(* activity	MB %	Total CK—(* activity	MB %
Skeletal muscle	10 000	0	10 000	0	10 000	0—3
Heart	2.000	30	2.000	15	2.000	4—27
Stomach	1 000	0	400	■	200	2—6
Uterus	500	0	—	—	60	2—20
Brain	200	0	500	0	700	0
Thyroid	50	0	—	—	200	6
Kidney	10	0	20	0	10	0
Liver	2	0	5	0	1	0
Lung	—	—	40	0	50	0—4
Spleen	—	—	5	0	5	0

\*) Total Ch. tissue activity is expressed as relative total CK activity per gm tissue. The activity in skeletal muscle is set at 10 000 units per gm tissue

### Tissue distribution of CK isoenzymes

Table I shows the human tissue CK isoenzyme distribution according to Jockers Wretou and Pfeleiderer (30), Roberts and associates (56) and Ogunro and associates (54). The total Ch. activity is expressed as relative CK activity per gm of tissue, and the activity of skeletal muscle is set at 10.000 units per gm tissue. As can be seen there is a substantial discrepancy concerning the total CK activity and the percentage of Ch—MB in most tissues except heart between the three references. Roberts and associates (56) using an ion exchange technique and Ogunro and associates (54) using an electrophoretic technique, found Ch—MB activity only in the heart muscle. In contrast, Jockers Wretou and Pfeleiderer (30) using an immunological technique, found

Ch—MB activity also in skeletal muscle, stomach, uterus, thyroid, and lung. But the total CK activity in these tissues, except in skeletal muscle, is low. A small proportion of Ch—MB activity in skeletal muscle with high total Ch. activity and a large muscle mass might therefore be a source of error in the evaluation of an elevated Ch—MB activity (77). Furthermore Ch—MB activity has also been found in skeletal muscle in earlier studies (13, 22, 62, 73).

### Clinical use of CK-MB

No CK—MB activity was found in sera from healthy persons, according to three studies (30, 54, 57), but Mercer and Varat (47) found 0—2 per cent Ch—MB activity in similar sera compared to 4.5—20 per cent after AMI. These authors also found a

CK—MB activity of 0—1.6 per cent in sera from postoperative patients, patients with renal failure, pneumonia, chronic lung disease, psychosis, cirrhosis, and from alcoholics. The total CK activity here was in the same range as after AMI. Smith and associates (63) reported elevated CK—MB activity in single cases of paroxysmal atrial fibrillation, pericarditis, and unexplained chest pain. Elevated CK—MB activity was detected consistently after cardiac surgery (10). In muscular dystrophy an elevated CK—MB activity was also reported, but was interpreted as heart muscle involvement (22). In contrast, no elevation of CK—MB activity was reported in association with noncardiac surgery (23), congestive heart failure without AMI (57), cardiac catheterization (57), intramuscular injections (33), or skeletal muscle trauma (57). In association with electrical countershock, modest elevation of CK—MB activity occurred in 6 per cent of the patients (19).

Va Der Veen and Willebrands (73) first reported an elevation of CK—MB activity in patients with AMI. Several reports have confirmed this finding (35, 56, 63, 70).

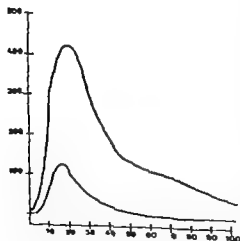


Fig. 1 A typical total-CK and CK—MB activity curve seen for an uncomplicated acute myocardial infarction. Hours on the abscissa and enzyme activity on the ordinate.

Figure 1 shows a typical CK—MB activity curve seen after an uncomplicated AMI. CK—MB activity exceeds the normal range within 4 hours after onset of symptoms, reaches a peak in an average of 15 hours, and declines to the normal range within 36 hours (4). The relative CK—MB activity at the peak has been reported to be 3—30 per cent of total CK activity (30, 57, 63). CK—MB reaches its peak value slightly earlier and declines more rapidly than total CK because of a somewhat higher fractional disappearance rate compared to those of CK—MM and total CK. This short duration of rise might limit the use of CK—MB, especially in patients with long delay between onset of symptoms and admittance to hospital. On the other hand, this could be an advantage, as a extension of an existing infarct might be discovered as a secondary rise in CK—MB activity. Furthermore, CK—MB could be of value in early diagnosis and early exclusion of an AMI.

#### A comparison of the different enzyme tests

There are several series that compare different enzymes in the diagnosis of AMI. All have the limitation of not absolutely defining AMI. Furthermore, a still unsolved problem is whether a small rise in enzyme activity can derive from reversibly injured myocardial cells (3, 71). A review of 25 series including 2,583 patients was presented by Goldberg and Winfield (21) who compared ASAT, αHBD, and CK. Most of this series diagnosed AMI from the clinical picture and the electrocardiogram (ECG). In that review 91 per cent of patients with AMI were found to have an elevated ASAT activity compared with 96 per cent for αHBD and CK. Table II presents three other series that compare both the sensitivity and the specificity of ECG and different enzyme tests (7, 58, 70). In these three series, the reference to each diagnostic parameter is the sum of the other diagnostic parameters in the same series. Table III sums up the series. It includes 719 patients.

que to be twice as high as the other two techniques. Thus, it seems reasonable to explain much of the discrepancy in the literature concerning CK-MB activity by methodological differences.

Moreover, most of the described methods

are technically complicated and time consuming, and thus limits their clinical use. However, recently a promising immunological technique using anti M antibodies has been presented (80), but it still needs further clinical evaluation.

Table I

Human tissue CK-MB distribution according to three references

Tissue	Ogunro et al, 1977		Roberts et al, 1975		Jockers Wretou & Pfeleiderer 1975	
	Total CK-(*) activity	MB %	Total CK-(*) activity	MB %	Total CK-(*) activity	MB %
Skeletal muscle	10 000	0	10 000	0	10 000	0-3
Heart	2 000	30	2 000	15	2 000	4-27
Stomach	1 000	0	400	0	200	2-6
Uterus	500	0	—	—	60	2-20
Brain	200	0	500	0	700	0
Thyroid	50	0	—	—	200	6
Kidney	10	0	20	0	10	0
Liver	2	0	5	0	1	0
Lung	—	—	40	0	50	0-4
Spleen	—	—	5	0	5	0

\*) Total CK tissue activity is expressed as relative total CK activity per gm tissue. The activity in skeletal muscle is set at 10 000 units per gm tissue.

### Tissue distribution of CK isoenzymes

Table I shows the human tissue CK isoenzyme distribution according to Jockers Wretou and Pfeleiderer (30), Roberts and associates (56), and Ogunro and associates (54). The total CK activity is expressed as relative CK activity per gm of tissue and the activity of skeletal muscle is set at 10 000 units per gm tissue. As can be seen, there is a substantial discrepancy concerning the total CK activity and the percentage of CK-MB in most tissues except heart between the three references. Roberts and associates (56), using an ion exchange technique and Ogunro and associates (54) using an electrophoretic technique, found CK-MB activity only in the heart muscle. In contrast, Jockers Wretou and Pfeleiderer (30) using an immunological technique found

CK-MB activity also in skeletal muscle, stomach, uterus, thyroid, and lung. But the total CK activity in these tissues, except in skeletal muscle, is low. A small proportion of CK-MB activity in skeletal muscle with high total CK activity and a large muscle mass might therefore be a source of error in the evaluation of an elevated CK-MB activity (77). Furthermore, CK-MB activity has also been found in skeletal muscle in earlier studies (13, 22, 62, 73).

### Clinical use of CK-MB

No CK-MB activity was found in sera from healthy persons, according to three studies (30, 34, 57) but Mercer and Varat (47) found 0-2 per cent CK-MB activity in similar sera compared to 4.5-20 per cent after AMI. These authors also found a

CK—MB activity of 0—1.6 per cent in sera from postoperative patients, patients with renal failure, pneumonia, chronic lung disease, psychosis, cirrhosis, and from alcoholics. The total CK activity here was in the same range as after AMI. Smith and associates (63) reported elevated CK—MB activity in single cases of paroxysmal atrial fibrillation, pericarditis, and unexplained chest pain. Elevated CK—MB activity was detected consistently after cardiac surgery (10). In muscular dystrophy an elevated CK—MB activity was also reported, but was interpreted as a heart muscle involvement (22). In contrast, no elevation of CK—MB activity was reported in association with noncardiac surgery (23), congestive heart failure without AMI (57), cardiac catheterization (57), intramuscular injections (33), or skeletal muscle trauma (57). In association with electrical counter shock, modest elevation of CK—MB activity occurred in 6 per cent of the patients (19).

Van Der Voorn and Willebrands (73) first reported an elevation of CK—MB activity in patients with AMI. Several reports have confirmed this finding (35, 56, 63, 70).

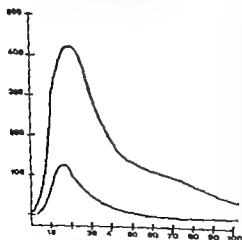


Fig. 1 A typical total-CK and CK—MB activity curve seen after an uncomplicated acute myocardial infarction. Hours on the abscissa and enzyme activity on the ordinate.

Figure 1 shows a typical CK—MB activity curve seen after an uncomplicated AMI. CK—MB activity exceeds the normal range within 4 hours after onset of symptoms, reaches a peak in an average of 15 hours, and declines to the normal range within 36 hours (4). The relative CK—MB activity at the peak has been reported to be 3—30 per cent of total CK activity (30, 57, 63). CK—MB reaches its peak value slightly earlier and declines more rapidly than total CK because of a somewhat higher fractional disappearance rate compared to those of CK—MM and total CK. This short duration of rise might limit the use of CK—MB, especially in patients with long delay between onset of symptoms and admittance to hospital. On the other hand, this could be an advantage, as extension of an existing infarct might be discovered as a secondary rise in CK—MB activity. Furthermore, CK—MB could be of value in early diagnosis and early exclusion of an AMI.

#### A comparison of the different enzyme tests

There are several series that compare different enzymes in the diagnosis of AMI. All have the limitation of not absolutely defining AMI. Furthermore, still unsolved problem is whether small rise in enzyme activity can derive from reversibly injured myocardial cells (3, 71). A review of 25 series including 2,585 patients was presented by Goldberg and Winfield (21) who compared ASAT, αHBD, and CK. Most of this series diagnosed AMI from the clinical picture and the electrocardiogram (ECG). In that review 91 per cent of patients with AMI were found to have an elevated ASAT activity compared with 96 per cent for αHBD and CK. Table II presents three other series that compare both the sensitivity and the specificity of ECG and different enzyme tests (7, 38, 70). In these three series, the reference to each diagnostic parameter is the sum of the other diagnostic parameters in the same series. Table III sums up the series; it includes 719 patients.

Table II

Comparison between different diagnostic parameters in three different series

Reference	Parameter	Sensitivity (%)	Specificity (%)
Wagner et al, 1973	ECG	66	100
	LD <sub>T</sub>	90	95
	CK	98	88
	CK—MB	100	99
Blomberg et al 1975	ECG	64	100
	ASAT	100	90
	LD <sub>T</sub>	98	91
	CK	100	89
	CK—MB	95	100
Roark et al 1976	ECG	78	100
	ASAT/LD	98	89
	CK	100	65
	CK—MB	96	100

According to Smith and associates (63) CK—MB is a more sensitive indicator of myocardial damage than enzyme tests hitherto available, but as Table III shows, the sensitivity of the different tests are fairly similar and outstanding compared with ECG. An even more sensitive method for determination of CK—MB activity would probably be of value for detecting small amounts of myocardial damage. Furthermore, the sensitivity of an enzyme test as a diagnostic of AMI can also be increased by shortening the sampling intervals (50, 67).

CK—MB isoenzyme has been said to be "cardiospecific" (22, 47, 59, 73) and as

Table III shows the specificity of ECG and CK—MB is set at 100 per cent. This specificity is clearly superior to the other enzyme tests. However ASAT "heart" LD and CK might individually lack specificity but the combination of these enzyme tests with the addition of alaninaminotransferase (ALAT GPT) will probably give a specificity almost equal to CK—MB. Moreover this combination of conventional enzyme tests can also give important information about complications of the AMI such as liver congestion.

At present, CK—MB is the single most specific test for AMI but it must not be regarded as truly specific for the myocardium. As pointed out in this review elevation of CK—MB activity has been reported in conditions other than AMI or heart diseases. There is still a great discrepancy in the literature concerning the CK—MB activity in different tissues, and the practical implication of a potential CK—MB activity in skeletal muscle has already been discussed. However this single enzyme specificity makes the test unique in the diagnosis of AMI in association with non-cardiac surgery in states of shock, and in other clinical states, when the conventional enzyme tests are disturbed (63).

Table III

Comparison between different diagnostic parameters. The sum of the three series presented in Table II ( $n = 719$ )

Parameter	Sensitivity %	Specificity %
ECG	69	100
ASAT	99	89
"heart" LD	95	92
CK	100	80
CK—MB	97	100

## Conclusions

A review of the literature of CK—MB suggests that

- 1) CK—MB is a sensitive test in diagnosis of AMI, limited by its short duration of rise.
- 2) CK—MB is today the single most specific enzyme test for AMI most suited in diagnosis of AMI in various clinical situations when the conventional enzyme tests are disturbed.
- 3) The early rise and short half life of CK—MB might be of value in early diagnosis and early exclusion of AMI. Furthermore, these qualities might also be of value in studies of the evolution of AMI.
- 4) There is still considerable discrepancy in the literature concerning the CK—MB activity in different human tissues. This could be due, at least in part, to methodological differences. At present CK—MB should not be considered as 100 per cent heart specific.
- 5) A rapid and simple method for separation and quantitation of CK—MB is needed to permit more widespread use of this isoenzyme.
- 6) More clinical experience is needed for further evaluation of this test.

## References

1. Acheson, J. James, D. C., Hutchinson, E. C., Wetherhead, R. Serum creatine kinase levels in cerebral vascular disease. *Lancet* 1: 1306, 1965.
2. Agnew, C. M. E. situation of the transaminase est. *Am. J. Cardiol.* 3: 74, 1959.
3. Ahmed, S. A., Williamson, J. R., Roberts, R., Clark, R. E., Sobel, B. E. The association of increased plasma MB CPh activity and irreversible ischemic myocardial injury in the dog. *Circulation* 54: 1117, 1976.
4. Ahumada, G., Roberts, R., Sobel, B. E. Evaluation of myocardial infarction with enzyme indices. *Prog. Cardiovasc. Dis.* 18: 405, 1976.
5. Batsakis, J. G., Briere, R. O. LDH isoenzymes by urea inhibition and substrate (lactate) modification. A clinical evaluation. *Clin. Biochem.* 2: 171, 1969.
6. Batsakis, J. G., Briere, R. O., Markel, S. F. *Diagnostic enzymology*. Am. Soc. Clin. Path., Chicago, 1970.
7. Blomberg, D. J., Kimber, W. D., Burke, M. D. Creatine kinase isoenzymes. Predictive value in the early diagnosis of acute myocardial infarction. *Amer. J. Med.* 59: 464, 1975.
8. Burger, A., Richterich, R., Aebi, H. Die Heterogenität der Kreatin-Kinase. *Biochem. Z.* 339: 305, 1964.
9. Cohen, L., Djordjević, J., Ornstejn, V. Serum lactic dehydrogenase isoenzyme patterns in cardiovascular and other diseases, with particular reference to acute myocardial infarction. *J. Lab. Clin. Med.* 64: 355, 1964.
10. Coleman, R. E., Klein, M. S., Roberts, R., Sobel, B. E. Improved detection of myocardial infarction with technetium-99m stannous pyrophosphate and serum MB creatine phosphokinase. *Amer. J. Cardiol.* 37: 732, 1976.
11. Coodley, E. L. Enzyme profiles in the evaluation of pulmonary infarction. *JAMA* 207: 1307, 1969.
12. Dawson, D. M., Eppenberger, H. M., Kaplan, N. O. Creatine kinase: Evidence for dimeric structure. *Biochem. Biophys. Res. Comm.* 21: 346, 1965.
13. Dawson, D. M., Fine, I. H. Creatine kinase in human tissues. *Arch. Neurol.* 16: 175, 1967.
14. DeRitis, F., Caltori, M., Guisti, G. Attività transaminasica del siero umano nell'epatite virale. *Minerva Med.* 46: 1207, 1955.
15. Deul, D. H., van Breeman, J. F. L. Electrophoresis of creatine phosphokinase from various organs. *Clin. Chim. Acta* 10: 276, 1964.

- 16 Dixon, S H Fuchs, J C. A., Ebert, P A Changes in serum creatine phosphokinase activity following thoracic, cardiac, and abdominal operations. *Arch. Surg* 103 66, 1971
- 17 Dreyfus, J.-Cl., Schapira, G., Scebat, L., Renaud, J Lenègre, J Les enzymes sériques dans le diagnostic des lésions myocardiques d'origine coronarienne. *Arch. Mal. Coer* 2 187 1960
- 18 Ebashi, S., Toyokura, Y., Momoi, H., Sugita, H. High creatine phosphokinase activity of sera of progressive muscular dystrophy *J Biochem.* 46 103 1959
- 19 Ehsani, A., Ewy G A Sobel B E. Effects of electrical countershock on serum creatine phosphokinase (CPK) isoenzyme activity *Amer J Cardiol* 37 12 1976
- 20 Forster G Escher J: Die Kreatin phosphokinase in der Diagnostik von Herzinfarkt und Myopathien *Helv Med. Acta* 28 513 1961
- 21 Goldberg D M., Winfield, D A. Diagnostic accuracy of serum enzyme assays for myocardial infarction in a general hospital population. *Brit. Heart J* 34 597 1972.
- 22 Goto, I Creatine phosphokinase isoenzymes in neuromuscular disorders. *Arch. Neur* 31: 116, 1974
- 23 Gowda, K. S., Roberts, R., Sobel B E. Detection of myocardial infarction with serum CPK isoenzymes in surgical patients (abstr) *Circulation* 50 (suppl III) III-109 1974
- 24 Graig, F A., Ross, G Serum creatine phosphokinase in thyroid disease. *Metabolism* 12 57 1963
- 25 Griffiths, P D Serum enzymes in diseases of the thyroid gland. *J Clin. Path* 18 660 1965
- 26 Griffiths, P D Serum creatine kinase and exercise. *Brit. Med. J* 2: 167 1965
- 27 Griffiths, P D ATP Creatine phosphotransferase in the diagnosis of acute chest pain. *Brit. Heart J* 28: 199 1966
- 28 Henry P D., Roberts, R Sobel B. E.: Rapid separation of plasma creatine kinase isoenzymes by batch adsorption on glass beads *Clin. Chem* 21 844 1975
- 29 Hess, J W., MacDonald, R. P., Fredrick, R. J., Jones, R. N Neely J Gross, D Serum creatine phosphokinase (CPK) activity in disorders of heart and skeletal muscle. *Ann. Intern. Med.* 61: 1015 1964
- 30 Jolkers-Wretou E., Pfeleiderer G Quantitation of creatine kinase isoenzymes in human tissues and sera by an immunological method. *Clin. Chim. Acta* 58 223 1975
- 31 Kar N C., Pearson, C. M. Activation of creatine phosphokinase by sulfhydryl compounds in normal and muscular dystrophy sera. *Proc. Soc. Exper Biol Med.* 118 662 1965
- 32 Karmen, A., Wroblewski, F La Due, J S Transaminase activity in human blood. *J Clin Invest.* 34: 126, 1954
- 33 Klein M. S., Shell, W E., Sobel, B. E. Serum creatine phosphokinase (CPK) isoenzymes after intramuscular injections, surgery and myocardial infarction *Cardiovasc. Res.* 7 412, 1973
- 34 Kontinen, A., Halonen, P I Serum creatine phosphokinase and  $\alpha$ -hydroxy butyric dehydrogenase activities compared with GOT and LDH in myocardial infarction. *Cardiologia, Basel* 43: 56 1963
- 35 Kontinen A Somer H Determination of serum creatine kinase isoenzymes in myocardial infarction *Amer J Cardiol* 29: 817 1972.
- 36 Kontinen, A., Somer H Specificity of serum creatine kinase isoenzymes in diagnosis of acute myocardial infarction. *Brit. Med J* 1 386, 1973
- 37 Kontinen, A., Veikko, H Louhija A Härtel G Origin of elevated serum enzyme activities after direct current counter-shock. *New Engl J Med.* 281: 231 1969

38. Kronberg, I. Hunt, D. Goble, A. J. Elevation of serum creatine phosphokinase levels after intramuscular injection of lidocaine. *Med. J. Aust.* 1: 635, 1975
39. Langer T. Levy R. I. Acute muscular syndrome associated with administration of clofibrate. *New Engl. J. Med.* 16: 856, 1968
40. Larsson-Cohn, U. Transaminase activity during oral contraceptive therapy. *Acta Obstet. Gynecol. Scand.* 45: 196, 1966.
41. Leana, J. I. King, B. D. Markello, R. Transaminase values following anesthesia and surgery. *New York J. Med.* 69: 2003 1969
42. Lohmann, K. Über die enzymatische Abspaltung der Kreatinphosphorsäure zugleich ein Beitrag zum Chemismus der Muskelkontraktion. *Biochem. Zisch* 271: 264 1934
43. MacLean, D. Griffiths, P. D. Emsie-Smith, D. Serum enzymes in relation to electrocardiographic changes in accidental hypothermia. *Lancet* 2: 1266, 1968
44. Markert, C. L. Lactate dehydrogenase isoenzymes. Dissociation and recombination of subunits. *Science* 140: 1329 1963
45. Meitzer H. Y. Mrozak, S., Boyer Effect of intramuscular injections on serum creatine phosphokinase activity. *Amer. J. Med. Sci.* 239: 42, 1970
46. Mercer D. Separation of tissue and serum creatine kinase isoenzymes by ion-exchange column chromatography. *Clin. Chem.* 20: 36, 1974
47. Mercer D. W. Varai, M. A. Detection of cardiac-specific creatine kinase isoenzyme in sera with normal or slightly increased total creatine kinase activity. *Clin. Chem.* 21: 1088, 1975
48. Muche D. D. Conley M. A., Carretta, R. F. Booth, R. W. Serum enzyme changes following cardiac catheterizations with and without selective coronary arteriography. *Amer. J. Med. Sci.* 260: 11 1970
49. Muggia, F. M., Ghossein, N. A., Hanck, A.: Creatine phosphokinase and other serum enzymes during radiotherapy. *JAMA* 211: 1345 1970
50. Nordlander R. Kreatinkinas vid akut hjärtinfarkt. Diagnostik och prognostik. Akademisk a handling, Stockholm, 1976.
51. Nydick, I. Taub J. Stollerman, G. J. et al. The influence of rheumatic fever on serum concentration of the enzyme glutamic oxaloacetic transaminase. *Circulation* 12: 795 1955
52. Nygren, A. Serum creatine phosphokinase activity in chronic alcoholism, in connection with acute alcohol intoxication. *Acta Med. Scand.* 179: 623 1966
53. Oguro, E. E., Peters, T. J. Hearse, D. J. Subcellular compartmentation of creatine kinase isoenzymes in guinea pig heart. *Cardiovasc. Res.* 11: 250, 1977
54. Oguro, E. A., Hearse, D. J. Shillingford, J. P. Creatine kinase isoenzymes, their separation and quantitation. *Cardiovasc. Res.* 11: 94 1977
55. Rao, P. S. Lakes, J. J. Ayres, S. M., Mueller H. New manual and automated method for determining activity of creatine kinase isoenzyme MB, by use of dihydrothreitol. *Clinical applications. Clin. Chem.* 21: 1612, 1975
56. Roberts, R., Henry P. D. Sobel, B. E. An improved basis for enzymatic estimation of infarct size. *Circulation* 52: 743 1975
57. Roberts, R., Gowda, K. S., Ludbrook, P. A. Sobel B. E. Specificity of leucylated serum MB creatine phosphokinase activity in the diagnosis of acute myocardial infarction. *Amer. J. Cardiol.* 36: 433 1975
58. Roark, S. F. Wagner G. S., Izlar H. L., Roe, C. R. Diagnosis of acute myocardial infarction in community hospital. Significance of CPK-MB determination. *Circulation* 53: 965 1976.



- 59 Roe C. R. Limbird L. L., Wagner G. S. Nerenberg S. T.: Combined isoenzyme analysis in the diagnosis of myocardial injury. Application of electrophoretic methods for the detection and quantitation of the creatine phosphokinase MB isoenzyme. *J. Lab. Clin. Med.* 80: 577 1972
- 60 Runde, L., Dale, J. Serum enzymes in acute tachycardia. *Acta Med. Scand.* 179: 535 1966
- 61 Sjövall K., Voigt, A. Creatine phosphotransferase isoenzyme. *Nature* 202: 701 1964
- 62 Smith, A. F. Separation of tissue and serum creatine kinase isoenzymes on polyacrylamide gel slabs. *Clin. Chim. Acta* 39: 351 1972
- 63 Smith, A. F., Radford, D., Wong C. P., Oliver M. F. Creatine kinase MB isoenzyme studies in diagnosis of myocardial infarction. *Brit. Heart J.* 38: 225 1976
- 64 Sobel B. E., Shell W. E. Serum enzyme determinations in the diagnosis and assessment of myocardial infarction. *Circulation* 45: 471 1972.
- 65 Sobel B. E., Shell W. E. Diagnostic and prognostic value of serum enzyme changes in patients with acute myocardial infarction. In Yu P. N., Goodwin J. F. (eds.) *Progress in Cardiology* 4: 1975
- 66 Somer H., Kontinen A. Demonstration of serum creatine kinase isoenzymes by a fluorescence technique. *Clin. Chim. Acta* 40: 133 1972
- 67 Sjöwe U. Early diagnosis of acute myocardial infarction. *Acta Med. Scand. Suppl.* 345 1973
- 68 Sørensen, N. S. Creatine phosphokinase in the diagnosis of myocardial infarction. *Acta Med. Scand.* 174: 725 1963
- 69 Wacker W. E. C., Rosenthal M., Snodgrass, P. J. et al.: A triad for the diagnosis of pulmonary embolism and infarction. *JAMA* 178: 8 1961
- 70 Wagner G. S., Roe C. R., Limbird, L. E., Rosat R. A., Wallace A. G.: The importance of identification of the myocardial — specific isoenzyme of creatine phosphokinase (MB form) in the diagnosis of acute myocardial infarction. *Circulation* 47: 263 1973
- 71 Waldenström, A.: Factors influencing experimental myocardial infarction. Thesis Gothenburg, Sweden, 1976.
- 72 Van der Helm H. J., Zondag, H. A., Hartog A. et al. Lactic dehydrogenase isoenzymes in myocardial infarction. *Clin. Chim. Acta* 7: 540, 1962.
- 73 Van der Veen A. J., Willebrands, A. F. Isoenzymes of creatine phosphokinase in tissue extracts in normal and pathological sera. *Clin. Chim. Acta* 13: 312, 1966
- 74 West, M., Gelb, D., Pilz, C. G. et al.: Serum enzymes in disease. VII. Significance of abnormal serum enzyme levels in cardiac failure. *Am. J. Med. Sci.* 241: 350, 1961
- 75 West, M., Eshchar J., Zimmerman, H. J. Serum enzymology in the diagnosis of myocardial infarction and related cardiovascular conditions. *Med. Clin. North Am.* 50: 171 1966
- 76 Vincent, W. R., Rapaport E.: Serum creatine phosphokinase in the diagnosis of acute myocardial infarction. *Amer. J. Cardiol.* 15: 17 1965
- 77 Witteveen, S. A. G. J. Lecture held in Gothenburg, Sweden, 1976
- 78 Wohlgemuth, J. Über eine neue Methode zur quantitativen Bestimmung des diastatischen Ferments. *Biochem. Ztschr.* 9: 1 1908
- 79 Wroblewski, F., LaDue, J. S.: Lactic dehydrogenase activity in blood. *Proc. Soc. Exptl. Biol. Med.* 90: 210, 1955
- 80 Würzburg, U., Hennrich, N., Lang, H., Prellwitz, W., Neumeier K., Kudel M.: Bestimmung der Aktivität von Creatinkinase MB im Serum unter Verwendung inhibierender Antikörper. *Klin. Wschr.* 54: 157 1976
- 81 Zener J. C., Harrison D. C. Serum enzyme values following intramuscular injection of lidocaine. *Arch. Intern. Med.* 134: 48 1974

# Radionuclides In acute myocardial Infarction

Jan Lessem

Heart section, Dept. of Medicine General Hospital  
MALMÖ SWEDEN

The history of cardiovascular nuclear medicine is intimately related to the development of nuclear medicine and to the desire of cardiologists to find procedures less traumatic than catheterizations (4-59). These factors combined with difficulties of diagnosing ischaemic heart diseases in some pa-

tients, due to previous pathological ECG and equivocal enzyme response, led to the use of radionuclide methods in this group of patients. Most patients with suspected acute myocardial infarction are usually immobile during the first phase of their disease and are monitored in coronary care unit.

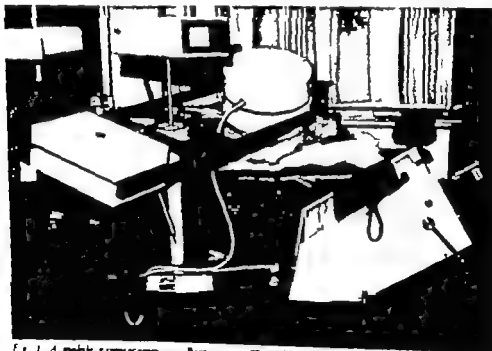


Fig 1 A mobile gammacamer — Portacamer II (General Electric) Beside examination is shown

- 59 Roe, C. R., Lambird, L. L., Wagner G. S., Verenberg, S. T. Combined isoenzyme analysis in the diagnosis of myocardial injury: Application of electrophoretic methods for the detection and quantitation of the creatine phosphokinase MB isoenzyme. *J. Lab. Clin. Med.* 80 577 1972.
- 60 Runde, I., Dale, J. Serum enzymes in acute tachycardia. *Acta Med. Scand.* 179 535 1966.
- 61 Sjövall, K., Voigt, A. Creatine phosphotransferase isoenzymes. *Nature* 202: 701 1964.
- 62 Smith, A. F. Separation of tissue and serum creatine kinase isoenzymes on polyacrylamide gel slabs. *Clin. Chim. Acta* 39 351 1972.
- 63 Smith, A. F., Radford, D., Wong, C. P., Oliver M. F. Creatine kinase MB isoenzyme studies in diagnosis of myocardial infarction. *Brit Heart J* 38 225 1976.
- 64 Sobel, B. E., Shell, W. E. Serum enzyme determinations in the diagnosis and assessment of myocardial infarction. *Circulation* 45 471 1972.
- 65 Sobel, B. E., Shell, W. E. Diagnostic and prognostic value of serum enzyme changes in patients with acute myocardial infarction, in Yu P. N. Goodwin, J. F. (eds.) *Progress in Cardiology* 4 1975.
- 66 Somer, H., Kontinen, A. Demonstration of serum creatine kinase isoenzymes by a fluorescence technique. *Clin. Chim. Acta* 40 133 1972.
- 67 Sjöwe, U. Early diagnosis of acute myocardial infarction. *Acta Med. Scand. Suppl.* 545 1973.
- 68 Sörensen, N. S. Creatine phosphokinase in the diagnosis of myocardial infarction. *Acta Med. Scand.* 174 725 1963.
- 69 Wacker, W. E. C., Rosenthal, M., Snodgrass, P. J. et al. A triad for the diagnosis of pulmonary embolism and infarction. *JAMA* 178 8 1961.
- 70 Wagner G. S., Roe, C. R., Lambird, L. E., Rosati, R. A., Wallace, A. G. The importance of identification of the myocardial — specific isoenzyme of creatine phosphokinase (MB form) in the diagnosis of acute myocardial infarction. *Circulation* 47 263, 1973.
- 71 Waldenström, A. Factors influencing experimental myocardial infarction. Thesis. Gothenburg, Sweden, 1976.
- 72 Van der Helm, H. J., Zondag, H. A., Hartog, A. et al. Lactic dehydrogenase isoenzymes in myocardial infarction. *Clin. Chim. Acta* 7 540 1962.
- 73 Van der Veen, K. J., Willebrands, A. F. Isoenzymes of creatine phosphokinase in tissue extracts in normal and pathological sera. *Clin. Chim. Acta* 13 312, 1966.
- 74 West, M., Gelb, D., Filz, C. G. et al. Serum enzymes in disease. VII. Significance of abnormal serum enzyme levels in cardiac failure. *Am. J. Med. Sci.* 241 350, 1961.
- 75 West, M., Esbchar, J., Zimmerman, H. J. Serum enzymology in the diagnosis of myocardial infarction and related cardiovascular conditions. *Med. Clin. North Am.* 50 171 1966.
- 76 Vincent, W. R., Rapaport, E. Serum creatine phosphokinase in the diagnosis of acute myocardial infarction. *Amer. J. Cardiol.* 15 17 1965.
- 77 Wittenveen, S. A. G. J. Lecture held in Gothenburg, Sweden, 1976.
- 78 Wohlgenuth, J. Über eine neue Methode zur quantitativen Bestimmung des diastatischen Ferments. *Biochem. Ztschr.* 9 1 1908.
- 79 Wroblewski, F., LaDue, J. S. Lactic dehydrogenase activity in blood. *Proc. Soc. Exptl. Biol. Med.* 90 210, 1955.
- 80 Würzburg, U., Hennrich, N., Lang, H., Prellwitz, W., Neumeier Kuedel, M. Bestimmung der Aktivität von Creatinkinase III im Serum unter Verwendung inhibierender Antikörper. *Klin. Wschr.* 54 357 1976.
- 81 Zetter, J. C., Harrison, D. C. Serum enzyme values following intramuscular injection of lidocaine. *Arch. Intern. Med.* 134 48, 1974.

# Radionuclides In acute myocardial infarction

Jan Lessem

Heart section Dept. of Medicine General Hospital  
MALMÖ SWEDEN

The history of cardiovascular nuclear medicine is intimately related to the development of nuclear medicine and to the desire of cardiologists to find procedures less traumatic than catheterizations (4-39). These factors combined with difficulties of diagnosing ischaemic heart diseases in some pa-

tients, due to previous pathological ECG and equivocal enzyme response, led to the use of radionuclide methods in this group of patients. Most patients with suspected acute myocardial infarction are usually immobile during the first phase of their disease and are monitored in a coronary care unit.



Fig. 1 A mobile gamma camera — Portacamer II (General Electric) Behind examination table.

- 59 Roe, C. R., Limbird, L. L., Wagner G S Nerenberg, S T Combined isoenzyme analysis in the diagnosis of myocardial injury Application of electrophoretic methods for the detection and quantitation of the creatine phosphokinase MB isoenzyme. *J Lab Clin Med.* 80 577 1972
- 60 Runde I., Dale, J Serum enzymes in acute tachycardia. *Acta Med. Scand.* 179 535 1966
- 61 Sjövall K., Voigt, A. Creatine phosphotransferase isoenzyme. *Nature* 202 701 1964
- 62 Smith, A. F Separation of tissue and serum creatine kinase isoenzymes on polyacrylamide gel slabs. *Clin. Chim. Acta* 39 351 1972.
- 63 Smith, A. F., Radford, D., Wong C. P Oliver M F Creatine kinase MB isoenzyme studies in diagnosis of myocardial infarction. *Brit Heart J* 38 225 1976
- 64 Sobel B E., Shell W E. Serum enzyme determinations in the diagnosis and assessment of myocardial infarction. *Circulation* 45 471 1972
- 65 Sobel B E., Shell W E. Diagnostic and prognostic value of serum enzyme changes in patients with acute myocardial infarction in Yu PN Goodwin, J F (eds.) *Progress in Cardiology* 4 1975
- 66 Somer H Kontinen, A : Demonstration of serum creatine kinase isoenzymes by a fluorescence technique. *Clin. Chim. Acta* 40 133 1972.
- 67 Säwe U Early diagnosis of acute myocardial infarction. *Acta Med. Scand. Suppl.* 545 1973
- 68 Sørensen, N S : Creatine phosphokinase in the diagnosis of myocardial infarction *Acta Med. Scand.* 174: 725 1963
- 69 Wacker W E. C., Rosenthal, M Snodgrass, P J et al A triad for the diagnosis of pulmonary embolism and infarction. *JAMA* 178 8 1961
- 70 Wagner G S. Roe, C. R., Limbird, L. E., Rozati, R A Wallace, A. G The importance of identification of the myocardial — specific isoenzyme of creatine phosphokinase (MB form) in the diagnosis of acute myocardial infarction *Circulation* 47: 263 1973
- 71 Waldenström, A.: Factors influencing experimental myocardial infarction. Thesis. Gothenburg, Sweden, 1976
- 72 Van der Helm, H. J., Zondag, H. A., Hartog, A. et al Lactic dehydrogenase isoenzymes in myocardial infarction. *Clin. Chim. Acta* 7: 340 1962.
- 73 Van der Veen K J Willebrands, A. F Isoenzymes of creatine phosphokinase in tissue extracts in normal and pathological sera. *Clin. Chim. Acta* 13 312, 1966
- 74 West, M., Gelb, D Pilz, C. G et al Serum enzymes in disease. VII Significance of abnormal serum enzyme levels in cardiac failure. *Am. J Med Sci.* 241 350 1961
- 75 West, M Eshchar J Zimmerman, H J Serum enzymology in the diagnosis of myocardial infarction and related cardiovascular conditions. *Med. Clin. North Am.* 50 171 1966
- 76 Vincent, W R Rapaport, E. Serum creatine phosphokinase in the diagnosis of acute myocardial infarction. *Amer J Cardiol* 15 17 1965
- 77 Witteveen, S A. G J Lecture held in Gothenburg, Sweden, 1976
- 78 Wohlgenuth, J : Über eine neue Methode zur quantitativen Bestimmung des diastatischen Ferments *Biochem. Ztschr* 9 1 1908
- 79 Wroblewski, F LaDue, J S : Lactic dehydrogenase activity in blood. *Proc. Soc. Exptl Biol. Med.* 90 210, 1955
- 80 Würzburg, U., Hennrich, N Lang, H., Prellwitz, W., Neumeier Kuedel, M. Bestimmung der Aktivität von Creatinkinase MB im Serum unter Verwendung inhibierender Antikörper *Klin. Wschr* 54 357 1976
- 81 Zener J C., Harrison, D C. Serum enzyme values following intramuscular injection of lidocaine. *Arch Intern. Med.* 134 48, 1974

# Radionuclides in acute myocardial infarction

Jan Lessem

Heart section, Dept. of Medicine General Hospital  
MALMÖ SWEDEN

The history of cardiovascular nuclear medicine is intimately related to the development of nuclear medicine and to the desire of cardiologists to find procedures less traumatic than catheterizations (4-39). These factors combined with difficulties of diagnosing ischaemic heart diseases in some pa-

tients, due to previous pathological ECG and equivocal enzyme response, led to the use of radionuclide methods in this group of patients. Most patients with suspected acute myocardial infarction are usually immobile during the first phase of their disease and are monitored in a coronary care unit.



Fig. 1. A mobile gamma camera — Potacameter II (General Electric). Bedside examination is shown.

- 59 Roe, C. R., Limbird, L. L., Wagner G S., Nerenberg S. T: Combined isoenzyme analysis in the diagnosis of myocardial injury. Application of electrophoretic methods for the detection and quantitation of the creatine phosphokinase MB isoenzyme. *J Lab Clin Med.* 80: 577 1972
- 60 Runde, I., Dale, J. Serum enzymes in acute tachycardia. *Acta Med. Scand.* 179 535 1966
- 61 Sjövall H., Voigt, A. Creatine phosphotransferase isoenzyme. *Nature* 202 701 1964
- 62 Smith A. F: Separation of tissue and serum creatine kinase isoenzymes on polyacrylamide gel slabs. *Clin Chim. Acta* 39 351 1972.
- 63 Smith, A. F., Radford, D. Wong, C. P., Oliver M. F. Creatine kinase MB isoenzyme studies in diagnosis of myocardial infarction. *Brit Heart J* 38 225 1976
- 64 Sobel B E., Shell W E. Serum enzyme determinations in the diagnosis and assessment of myocardial infarction. *Circulation* 45: 471 1972.
- 65 Sobel B E., Shell, W E.: Diagnostic and prognostic value of serum enzyme changes in patients with acute myocardial infarction, in Yu PN Goodwin J F (eds.) *Progress in Cardiology* 4 1975
- 66 Somer H Kontanen, A. Demonstration of serum creatine kinase isoenzymes by a fluorescence technique. *Clin. Chim. Acta* 40: 133 1972
- 67 Sjöwe U. Early diagnosis of acute myocardial infarction. *Acta Med Scand Suppl* 545 1973
- 68 Sorensen N S. Creatine phosphokinase in the diagnosis of myocardial infarction *Acta Med Scand* 174 725 1963
- 69 Wacker W E. C., Rosenthal M Snodgrass, P J et al. A triad for the diagnosis of pulmonary embolism and infarction. *JAMA* 178 8 1961
- 70 Wagner G S. Roe, C. R., Limbird, L. E. Rosati, R A., Wallace A G. The importance of identification of the myocardial — specific isoenzyme of creatine phosphokinase (MB form) in the diagnosis of acute myocardial infarction. *Circulation* 47 263 1973
- 71 Waldenström, A. Factors influencing experimental myocardial infarction. Thesis. Gothenburg Sweden 1976.
- 72 Van der Helm H. J. Zondag, H. A., Hartog, A et al: Lactic dehydrogenase isoenzymes in myocardial infarction. *Clin. Chim. Acta* 7: 540, 1962.
- 73 Van der Veen, h. J. Willebrands, A. F. Isoenzymes of creatine phosphokinase in tissue extracts in normal and pathological sera. *Clin. Chim Acta* 13 312 1966
- 74 West, M. Gelb, D., Pilz, C. G. et al. Serum enzymes in disease. VII. Significance of abnormal serum enzyme levels in cardiac failure. *Am. J Med. Sci.* 241: 350, 1961
- 75 West, M. Eshchar J., Zimmerman, H. J. Serum enzymology in the diagnosis of myocardial infarction and related cardiovascular conditions. *Med. Clin North Am.* 50 171 1966.
- 76 Vincent, W R., Rapaport, E. Serum creatine phosphokinase in the diagnosis of acute myocardial infarction. *Amer J Cardiol* 15 17 1965
- 77 Witteveen S. A. G. J.: Lecture held in Gothenburg Sweden, 1976
- 78 Wohlgemuth, J. Über eine neue Methode zur quantitativen Bestimmung des diastatischen Ferments. *Biochem. Ztschr* 9 1 1908
- 79 Wroblewski, F. LaDue, J S. Lactic dehydrogenase activity in blood. *Proc. Soc. Exptl Biol. Med.* 90 210, 1955
- 80 Würzburg U. Hennrich, N. Lang, H., Prellwitz, W., Neumeier Kuedel M.: Bestimmung der Aktivität von Creatinkinase MB im Serum unter Verwendung inhibierender Antikörper. *Klin Wschr* 54 357 1976
- 81 Zener J C., Harrison, D. C.: Serum enzyme values following intramuscular injection of lidocaine. *Arch Intern. Med.* 134 48 1974

# Radionuclides in acute myocardial infarction

Jan Lessem

Heart section Dept. of Medicine General Hospital,  
MALMÖ SWEDEN

The history of cardiovascular nuclear medicine is intimately related to the development of nuclear medicine and to the desire of cardiologists to find procedures less traumatic than catheterizations (4-39). These factors combined with difficulties of diagnosing ischaemic heart diseases in some pa-

tients, due to previous pathological ECG and equivocal enzyme response, led to the use of radionuclide methods in this group of patients. Most patients with suspected acute myocardial infarction are usually immobile during the first phase of their disease and are monitored in coronary care unit.

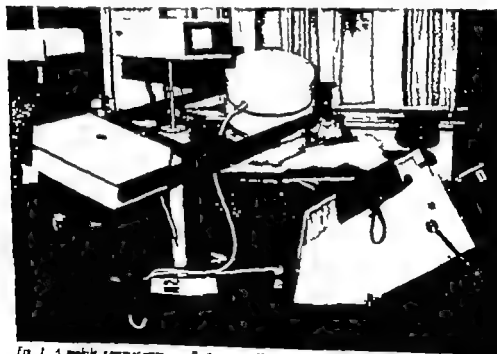


Fig 1 A mobile gamma-camera — Portacamera II (General Electric) Bedside examination



Radionuclide methods were not available to the cardiologist, despite the development of better radiopharmaceuticals, until the recent development of the mobile gamma camera (fig 1). This brought bedside nuclear medicine into the coronary care unit (45).

The employment of radionuclide methods in the diagnosis and evaluation of patients with acute myocardial infarction followed mainly three directions (Table I).

**Table 1 Methods used in cardiovascular nuclear medicine**

- 1 Positive infarct scintigraphy — substances accumulating in necrotic myocardium
    - $^{203}\text{Hg}$  Mercurascan
    - $^{67}\text{Ga}$
    - $^{99\text{m}}\text{Tc}$  pyrophosphate
    - $^{99\text{m}}\text{Tc}$  tetracycline
    - $^{99\text{m}}\text{Tc}$ -glucoheptonate
  - 2 Negative infarct scintigraphy — substances accumulating in normal myocardium
    - $^{43}\text{K}$
    - $^{86}\text{Rb}$
    - $^{131}\text{Cs}$
    - $^{129}\text{Cs}$
    - $^{201}\text{Tl}$
    - $^{15}\text{NH}_4^+$
    - $^{54}\text{Mn}$
    - $^{11}\text{C}$  Palmitic acid
  - 3 Radiocardiography hemodynamic assessments
    - $^{99\text{m}}\text{Tc}$  human serum albumin
    - $^{99\text{m}}\text{Tc}$ -erythrocytes
- 1) "Positive" infarct scintigraphy with substances accumulating in infarcted myocardium. Among the first substances described were mercury isotopes, such as  $^{203}\text{Hg}$  tagged to hydroxymercurylfluorescein (33) which gave satisfactory results in dogs with induced acute infarct (18, 25–42) these never succeeded clinically. Recently a different group of substances, mainly phosphates labelled with  $^{99\text{m}}\text{Tc}$ , were shown to be clinically applicable in the diagnosis of acute myocardial infarction Bonte and coworkers (6)

showed that a pyrophosphate labelled with  $^{99\text{m}}\text{Tc}$  accumulated in acutely infarcted myocardium. Later others verified this (16, 28, 35, 56).  $^{99\text{m}}\text{Tc}$  pyrophosphate proved extremely useful in diagnosing peri- and postoperative myocardial infarctions (32, 41) in this clinical setting enzymes and ECG cannot be used after cardiac surgery.

$^{99\text{m}}\text{Tc}$ , obtained as a daughter product of  $^{99}\text{Mo}$ , has a half life of 6 hours and gamma ray energy of 147 keV. Thus it is suitable for the low energy mobile gamma cameras.

The mechanism behind the pyrophosphate uptake is obscure but it has been postulated that pyrophosphate has an affinity to hydroxyapatite crystals formed in the mitochondria when the myocardial cells undergo necrosis (8, 49, 50). Several groups (12, 20, 48) recently presented evidence that pyrophosphate is taken up mainly by irreversibly damaged myocardial cells. These might still have some perfusion left (55) thus enabling pyrophosphate to reach them.

Simultaneously with the development of  $^{99\text{m}}\text{Tc}$  pyrophosphate, other agents, such as  $^{99\text{m}}\text{Tc}$  tetracycline (23, 24) and later  $^{99\text{m}}\text{Tc}$ -glucoheptonate (26), were introduced as infarct labelling agents. However both these substances have largely been abandoned, as the interval between injection of the radionuclide and the imaging procedure was too long, allowing other parameters to provide the diagnosis.

- 2) "Negative" infarct scintigraphy using substances accumulating in normal myocardium. These radionuclides are believed to reflect regional myocardial perfusion, and when the perfusion is decreased, a perfusion defect appears in the scintigram. The substances in this group are potassium-43 (57) and its analogues. Several have been used, such as  $^{86}\text{Rb}$  (11),  $^{131}\text{Cs}$  (4, 12) and  $^{129}\text{Cs}$  (44). All of them had a gamma energy level more suitable for the rectilinear scanner than for the gamma camera, thus their clinical

cal applicability was limited. Recently another potassium analogue,  $^{201}\text{Tl}$ , was introduced (27) and proved to be a very useful tool in the diagnosis of acute myocardial infarction (19, 52, 54). It has two energy levels, (80 and 167 keV), both being ideal for the low energy mobile gamma cameras. The long half life (about 72 hours) eliminates the disadvantage of being a cyclotron produced product.

The potassium analogues reflect the function of the sodium-potassium pump within the myocardial cells. When the myocardium is perfused, a significant amount of potassium is withheld intracellularly. If the perfusion is decreased, the amount of available potassium is also decreased thus a perfusion defect in the scintigram will appear. From this, it is apparent that no differentiation of the age of the perfusion defect is possible with these radionuclides.

Mason and coworkers (34) showed that potassium or its analogues are largely extracted by the myocardium during the first circulatory pass, and when evenly mixed with the blood, are distributed proportionally to the cardiac output (46).

3) Radiocardiography where the left ventricular function and wall motion are studied. Ventricular function can be measured non-invasively by two methods. First by recording the initial passage of bolus injected blood pool tracer through the heart, first pass study which Ashburn and Schelbert utilized (47). The first pass method utilizes a recording of the time-activity curve over the left ventricle that has peaks and valleys corresponding to end-diastole and end-systole (Fig. 2).

Second by data recording after the tracer has equilibrated. An ECG-gate and the scintillation camera is used so that images

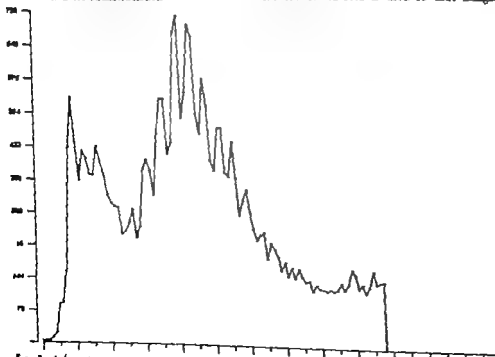


Fig. 2 A first pass curve amplified. The ejection fraction in this patient was calculated to be 41%.

Radionuclide methods were not available to the cardiologist, despite the development of better radiopharmaceuticals, until the recent development of the mobile gamma camera (fig 1) This brought bedside nuclear medicine into the coronary care unit (45)

The employment of radionuclide methods in the diagnosis and evaluation of patients with acute myocardial infarction followed mainly three directions (Table I)

**Table I Methods used in cardiovascular nuclear medicine**

- 1 Positive infarct scintigraphy — substances accumulating in necrotic myocardium
    - $^{203}\text{Hg}$  Mercurascan
    - $^{67}\text{Ga}$
    - $^{99\text{m}}\text{Tc}$  pyrophosphate
    - $^{99\text{m}}\text{Tc}$  tetracycline
    - $^{99\text{m}}\text{Tc}$ -glucoheptonate
  - 2 Negative infarct scintigraphy — substances accumulating in normal myocardium
    - $^{43}\text{K}$
    - $^{86}\text{Rb}$
    - $^{131}\text{Cs}$
    - $^{129}\text{Cs}$
    - $^{201}\text{Tl}$
    - $^{15}\text{NH}_4^+$
    - $^{54}\text{Mn}$
    - $^{14}\text{C}$  Palmitic acid
  - 3 Radiocardiography hemodynamic assessments
    - $^{99\text{m}}\text{Tc}$  human serum albumin
    - $^{99\text{m}}\text{Tc}$ -erythrocytes
- 1) Positive infarct scintigraphy with substances accumulating in infarcted myocardium. Among the first substances described were mercury isotopes, such as  $^{203}\text{Hg}$  tagged to hydroxymercurylfluorescein (33) which gave satisfactory results in dogs with induced acute infarct (18, 25, 42) these never succeeded clinically. Recently a different group of substances, mainly phosphates labelled with  $^{99\text{m}}\text{Tc}$ , were shown to be clinically applicable in the diagnosis of acute myocardial infarction Bonte and coworkers (6)

showed that a pyrophosphate labelled with  $^{99\text{m}}\text{Tc}$  accumulated in acutely infarcted myocardium. Later others verified this (16, 28, 35, 56)  $^{99\text{m}}\text{Tc}$  pyrophosphate proved extremely useful in diagnosing peri- and postoperative myocardial infarctions (32, 41) in this clinical setting, enzymes and ECG cannot be used after cardiac surgery

$^{99\text{m}}\text{Tc}$ , obtained as a daughter product of  $^{99}\text{Mo}$ , has a half-life of 6 hours and gamma ray energy of 147 keV. Thus it is suitable for the low energy mobile gamma cameras

The mechanism behind the pyrophosphate uptake is obscure, but it has been postulated that pyrophosphate has an affinity to hydroxyapatite crystals formed in the mitochondria when the myocardial cells undergo necrosis (8, 49, 50). Several groups (12, 20, 48) recently presented evidence that pyrophosphate is taken up mainly by irreversibly damaged myocardial cells. These might still have some perfusion left (55) thus enabling pyrophosphate to reach them.

Simultaneously with the development of  $^{99\text{m}}\text{Tc}$  pyrophosphate, other agents, such as  $^{99\text{m}}\text{Tc}$  tetracycline (23, 24) and later  $^{99\text{m}}\text{Tc}$ -glucoheptonate (26), were introduced as infarct labelling agents. However both these substances have largely been abandoned, as the interval between injection of the radionuclide and the imaging procedure was too long, allowing other parameters to provide the diagnosis.

- 2) "Negative" infarct scintigraphy using substances accumulating in normal myocardium. These radionuclides are believed to reflect regional myocardial perfusion, and when the perfusion is decreased, a perfusion defect appears in the scintigram. The substances in this group are potassium-43 (57) and its analogues. Several have been used, such as  $^{86}\text{Rb}$  (11),  $^{131}\text{Cs}$  (4, 12), and  $^{129}\text{Cs}$  (44). All of them had a gamma energy level more suitable for the rectilinear scanner than for the gamma camera thus their clinical

These techniques make possible early diagnosis of acute myocardial infarction (29). Willerson and coworkers found positive pyrophosphate scintigrams already 12 hours after the onset of symptoms. Wackers et al found that perfusion defects with  $^{201}\text{Tl}$  could be diagnosed as early as 6 hours after the onset of symptoms. In Wackers series all patients examined before 6 hours after the onset had developed perfusion defects in areas later corresponding to ECG-localization of the infarct (54).

### Clinical study

All these methods were used in patients admitted to the coronary care unit of the Malmö General hospital with primary clinical suspicion of acute myocardial infarction due to severe chest pain, pulmonary oedema, dysrhythmias, and dyspnoea.

The clinical diagnosis of acute myocardial infarction was based on any of the following criteria

- 1) Subjective symptoms in combination with typical QRST-changes in the ECG
- 2) Subjective symptoms in combination with two elevated enzyme values (S-ASAT S-LD)
- 3) Typical QRST-changes in the ECG in combination with two elevated enzyme values
- 4) Autopsy data (21/28)

In contrast, the diagnosis of unstable angina pectoris was based on a combination of the following criteria

- 1) Previous stable angina, or angina of recent onset with progressive increase in severity of symptoms
- 2) Anginal rest with recurrent episodes lasting more than 20 minutes and poorly relieved by nitrates
- 3) No elevation of serum enzymes
- 4) Transient ST-T changes that frequently return to normal after the attack (10/4)

All 350 patients were examined with 111 mCi  $^{201}\text{Tl}$ -pyrophosphate (Byk Mallinckrodt, USA, Solcosint, Kabi Diagnostics,

Diagnostics inc., USA) 125 patients were also in estrated with 1.5 mCi  $^{201}\text{Tl}$  (Phlips Duphar the Netherlands). In 48 patients, different hemodynamic evaluations were also made. A mobile gamma camera, Portacamara IIB or C (General Electric, USA) was used with a standard low-energy parallel hole collimator. The scintigrams were obtained in anterior — posterior left 30° anterior oblique and left lateral positions. All were evaluated for presence, absence, size, localization, and intensity of an uptake or defect. When radiocardiography was performed, the left ventricular ejection fraction was counted if a gated study was undertaken, the wall motion was estimated.

### Results

Of the 350 pyrophosphate examinations, 64 showed positive uptakes (Table II). In the group of 188 patients with acute transmural infarction, 180 showed radiotracer accumulation and well localized intense uptakes in 90 per cent. (Fig. 4). The cor-  
rel-



Fig 4 Myocardial scintigram with  $^{201}\text{Tl}$ -pyrophosphate recorded 90 minutes after injection, in LAO 30° position. A anterior grade 3 intense peak was recorded in the patient with transmural anterior infarct. The recording was made with the Portacamara IIB.



Fig 3 After injection of 15 mCi  $^{99m}\text{Tc}$ -human serum albumin gated study was performed in this patient. The upper panel illustrates end systole and the bottom panel illustrates end diastole. No aknetic area can be recognized.

are recorded during end systole and end diastole (40-43) (Fig 3). Gated studies have the advantage of being able to use several views after a single tracer injection, and are therefore more like regular angiography. Both methods can be used to calculate the left ventricular ejection fraction, according to the following formula:

$$\text{LVEF} = \frac{\text{EDV} - \text{ESV}}{\text{EDV}} - \text{BKG}$$

where

LVEF = left ventricular ejection fraction

EDV = end-diastole volume

ESV = end systolic volume

BKG = background

Several studies, independent (17) of each other have shown (17-51) correlation coefficients of 0.9 or better for ejection fractions obtained with radionuclide methods and angiography (37).

Impaired left ventricular function can then be diagnosed. Left ventricular wall motion is best studied with gated blood pool studies, where diagnosis of akinetic and dyskinetic areas can easily be made.

Both methods have the advantage of accumulating data over a relatively short time. This allows them to be used rather easily in the coronary care unit. They can very easily be repeated several times during the patient's stay in the ward, and thereby yield information of his day to day hemodynamic situation. It seems as though both methods, properly utilized, can predict left ventricular failure early (15-51) and also estimate the effect of treatment.

The indications for using radionuclide methods in cardiology are several and have been demonstrated by several reports. The following seem to be the major indications:

- Differentiation of origin of chest pain (47)
- Previous pathological ECG e.g., bundle branch block, remaining ST-T changes after previous infarcts in combination with chest pain postoperatively
- Differentiation between new and old infarcts (54)
- No adequate enzyme response, e.g., alcoholism, liver pathology postoperatively
- Hemodynamic assessment of the working capacity of the right and left ventricles during several phases of the infarct

Besides these, several reports by Botvinick and coworkers have shown that sizing of infarcted myocardium can be performed with  $^{99m}\text{Tc}$  pyrophosphate (7). Holman and coworkers recently confirmed these findings (22). These results suggest that in the future it will be possible to judge the efficiency of decreasing the size of a necrotic area by pharmacological or surgical interventions.

These techniques make possible early diagnosis of acute myocardial infarction (29). Willerson and coworkers found positive pyrophosphate scintigrams already 12 hours after the onset of symptoms. Wackers et al found that perfusion defects with  $^{201}\text{Tl}$  could be diagnosed as early as 6 hours after the onset of symptoms. In Wackers series all patients examined before 12 hours after the onset had developed perfusion defects in areas later corresponding to ECG-localization of the infarct (34).

### Clinical study

All these methods were used in patients admitted to the coronary care unit of the Malmö General hospital with primary clinical suspicion of acute myocardial infarction due to severe chest pain, pulmonary oedema, dysrhythmias, and dyspnoea.

The clinical diagnosis of acute myocardial infarction was based on any of the following criteria

- 1) Subjective symptoms in combination with typical QRST-changes in the ECG
- 2) Subjective symptoms in combination with two elevated enzyme hues (S-ASAT S-LD)
- 3) Typical QRST-changes in the ECG in combination with two elevated enzyme values
- 4) Autopsy data (21-28).

In contrast, the diagnosis of unstable angina pectoris was based on combination of the following criteria

- 1) Previous stable angina, or angina of recent onset with progressive increase in severity of symptoms
- 2) Angina at rest with recurrent episodes lasting more than 20 minutes and poorly relieved by nitrates
- 3) No elevation of serum enzymes
- 4) Transient ST-T changes that frequently return to normal after the attack (10, 4)

All 350 patients were examined with 111 mCi  $^{201}\text{Tl}$  pyrophosphate (Byk Mallinckrodt, USA, Solcosint, Kabi-Diagnostica,

Diagnostics inc., USA). 125 patients were also investigated with 1.5 mCi  $^{201}\text{Tl}$  (Philips Duphar the Netherlands). In 48 patients, different hemodynamic evaluations were also made. A mobile gamma camera, Portacamera 11B or C (General Electric, USA) was used with a standard low-energy parallel hole collimator. The scintigrams were obtained in anterior — posterior, left 30° anterior oblique and left lateral positions. All were evaluated for presence, absence, size, localization, and intensity of an uptake or defect. When radiocardiography was performed, the left ventricular ejection fraction was counted if gated study was undertaken, the wall motion was estimated.

### Results

Of the 350 pyrophosphate examinations, 264 showed positive uptakes (Table II). In the group of 188 patients with acute transmural infarction, 180 showed radiocardiologically well localized intense uptakes in 90 per cent. (Fig. 4). The correlation



Fig. 4 Myocardial scintigram with  $^{201}\text{Tl}$  pyrophosphate recorded 90 minutes after myocardial infarction in LAO 30° position. An anterior grade 3 intense plaque as recorded in the patient with transmural anterior infarct. The recording was made with the Portacamera 11

tion between the uptake localization and ECG localization of the infarct was excellent. All 5 patients with left bundle branch block but who fulfilled the criteria for acute myocardial infarction also exhibited well localized and intense pyrophosphate uptakes. The earliest uptake was registered in 10 patients examined 4 hours after the onset of symptoms.

Of the patients diagnosed as unstable angina pectoris, 73 per cent showed an uptake but this was distinctly different from the uptake in transmural infarcts, which also Ab ulla and coworkers found (1). These patients had low graded, diffusely spread uptakes (Fig 5).

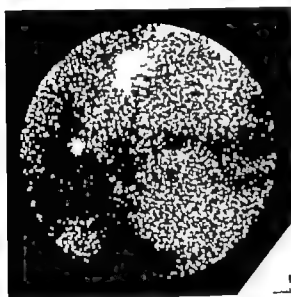


Fig 5 A 62 year old male with a diffuse low intense pyrophosphate uptake seen in combination with unstable angina pectoris

Positive uptakes were found in five patients with other cardiac diseases. One had Chagas disease (30) (Fig 6) and one, Prinzmetal variant angina. Two were found in patients with old infarcts and ventricular aneurysms, which also Ahmad (2) observed. The final positive pyrophosphate scintigrams were registered in a patient who developed an acute myocardial infarction after defibrillation (Fig 7) a finding previously reported by diCola and coworkers (14).

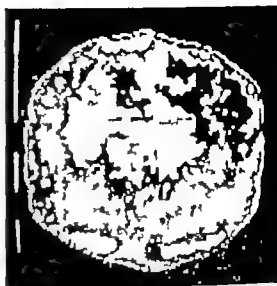


Fig 6 A b ge antero-lateral uptake with the intensity graded 3. The patient suffered from Chagas disease. The scintigram mimicked the pattern of transmural myocardial infarction.



Fig 7 A pyrophosphate uptake recorded in a patient after transthoracic counter current shock

125 patients were also examined with  $^{201}\text{Tl}$ . A very good correlation existed between a thallium defect and a pyrophosphate uptake (Fig 8). However seven Tl scintigrams showed perfusion defects where no new infarct could be verified in patients who had previously sustained infarcts.



Fig 8 An LAO 45° recording with  $^{201}\text{Tl}$  in patient with an inferior transmural infarct. In the pool re. Large perfusion defect is seen. The recording was made with Portacamera II 20 minutes after injection.

In 11 of them the pyrophosphate examination remained negative and one was questionably positive, probably owing to ventricular aneurysm. Five patients with unstable angina pectoris had perfusion defects (Fig. 9) thus making it impossible to

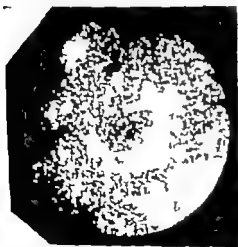


Fig 9 The LAO 45° recording with  $^{201}\text{Tl}$  in patient with unstable angina. Note the decreased perfusion in the antero-apical region.

separate them from those with acute myocardial infarction. A similar finding was recently reported by Wackers and coworkers (53). No false negative has been reported with  $^{201}\text{Tl}$ -scintigraphy.

Gated thallium studies have also been performed with a pin hole collimator (focusing on the septum) which has been utilized when septal infarcts or conduction disorders were present (Fig. 10).

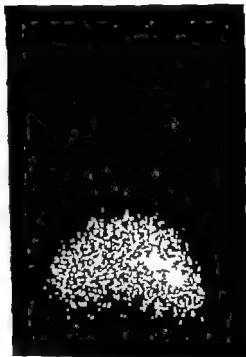


Fig 10 A gated  $^{201}\text{Tl}$ -study performed with pin hole collimator in patient with left bundle branch block. The upper panel illustrates end-systole and the lower end-diastole. In the lower panel perfusion defect is seen in the septal region.

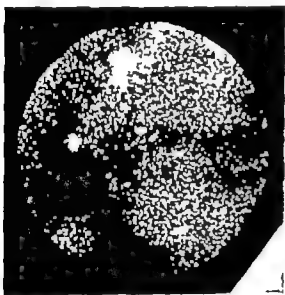
### Conclusions

It can be concluded that both  $^{32}\text{P}$ -pyrophosphate and  $^{201}\text{Tl}$  are useful aids in the diagnosis of acute myocardial infarction, as Parkey and several others have shown (29, 38, 5). Both methods have a high degree of



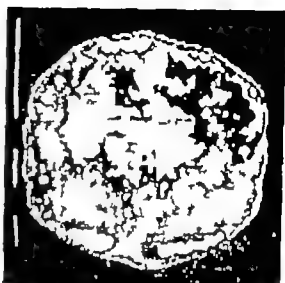
tion between the uptake localization and ECG localization of the infarct was excellent. All 5 patients with left bundle branch block, but who fulfilled the criteria for acute myocardial infarction also exhibited well localized and intense pyrophosphate uptakes. The earliest uptake was registered in 10 patients examined 4 hours after the onset of symptoms.

Of the patients diagnosed as unstable angina pectoris, 73 per cent showed an uptake but this was distinctly different from the uptake in transmural infarcts, which also Ab ulla and coworkers found (1). These patients had low graded, diffusely spread uptakes (Fig 5).



*Fig 5 A 62 year old male with a diffuse low intensity pyrophosphate uptake seen in combination with unstable angina pectoris*

Positive uptakes were found in five patients with other cardiac diseases. One had Chagas disease (30) (Fig 6) and one, Prinzmetal variant angina. Two were found in patients with old infarcts and ventricular aneurysms, which also Ahmad (2) observed. The final positive pyrophosphate scintigrams were registered in a patient who developed an acute myocardial infarction after defibrillation (Fig 7) a finding previously reported by diCola and coworkers (14).



*Fig 6 A huge antero-lateral uptake with the intensity graded 3. The patient suffered from Chagas disease. The scintigram mimicked the pattern of transmural myocardial infarction.*



*Fig 7 A pyrophosphate uptake recorded in a patient after an antithrombotic counter current shock.*

125 patients were also examined with  $^{201}\text{Tl}$ . A very good correlation existed between a thallium defect and a pyrophosphate uptake (Fig 8). However seven Tl scintigrams showed perfusion defects where no new infarct could be verified in patients who had previously sustained infarcts.

## References

- 1 Abdulla, A., Canedo, M., Cortez, B., McGinnis, K., Wilhelm, S.: Detection of unstable angina by  $^{99m}\text{Tc}$ -pyrophosphate myocardial scintigraphy. *Chest* 69: 168, 1976.
- 2 Ahmad, M., Dubiel, J., Verdon, T., Martin, R.: Technetium  $^{99m}$ -stannous pyrophosphate myocardial imaging in patients with and without left ventricular aneurysm. *Circulation* 53: 833 1976.
- 3 Ashburn, B., Kostok, W., Kartner, J., Peterson, K., Sobel, B.: Left ventricular volume and ejection fraction determination by radionuclide angiography. *Semin. Nucl. Med.* 3: 165 1973.
- 4 Berger, H., Freedman, G., Zaret, B.: Non invasive radionuclide imaging in the patient with cardiovascular disease. *Connecticut Medicine* 40: 311 1976.
- 5 Berger, H., Goetschalk, A., Zaret, B.: Radionuclide imaging of myocardial infarction in man. *J Nucl. Med.* 18: 594 1977.
- 6 Bonte, F., Parkey, R., Graham, R., Stokley, E., Moore, J.: A new method for radionuclide imaging of myocardial infarcts. *Radiology* 110: 473 1974.
- 7 Borwienek, E., Shames, D., Lippin, A., Tyberg, J., Townsend, R., Paimley, W.: Non invasive quantification of myocardial infarction with Technetium- $^{99m}$  pyrophosphate. *Circulation* 52: 909 1975.
- 8 Baji, M., Parkey, R., Dees, J., Stokley, E., Harris, R., Bonte, F., Wilkerson, J.: Morphologic correlates of technetium  $^{99m}$  stannous pyrophosphate imaging of acute myocardial infarcts in dogs. *Circulation* 52: 596, 1975.
- 9 Cabamon, J., Septfonds, J., Artus, J., Miro, L., Soucon, H.: Sémiologie scintigraphique de infarctus du myocarde. *J. de med. de Montpellier* 10: 3 1973.
- 10 Cairns, J., Fantus, I., Nisamen, G.: Unstable angina pectoris. *Amer Heart J* 92: 373, 1976.
- 11 Carr, E., Beierwaltes, W., Wegst, A., Bartlett, J. D.: Myocardial scanning with rubidium 86. *J Nucl. Med.* 3: 76, 1962.
- 12 Carr, E., Gleason, G., Shaw, J., Krantz, R.: Direct diagnosis of myocardial infarction by photon scanning after administration of cesium - 131. *Amer Heart J* 68: 627 1964.
- 13 Coleman, E., Klein, M., Ahmed, A., Weiss, E., Buchholz, W., Sobel, B.: Mechanisms contributing to myocardial accumulation of Technetium  $^{99m}$  Stannous pyrophosphate after coronary occlusion. *Amer J Card.* 39: 55 1977.
- 14 DiCola, V., Freedman, G., Downing, E., Zaret, B.: Myocardial uptake of technetium  $^{99m}$  Stannous pyrophosphate following direct current trans thoracic Countershock. *Circulation* 54: 940, 1976.
- 15 Duncan, B., Fulton, M., Morrison, S.C., Lutz, W., Donald, K., Kerr, F., Kirby, J., Julian, O., Oliver, M.: Prognosis of new and worsening angina pectoris. *Brit. Med. J* 1: 981 1976.
- 16 Ennis, J., Walsh, M., Mahon, J.: Value of I fartspecific Isotope ( $^{99m}\text{Tc}$  labelled stannous pyrophosphate) in myocardial scanning. *Brit. Med. J* 11: 517 1975.
- 17 Folland, E., Ritchie, J., Hamilton, G., Kennedy, J.: First pass and blood pool radionuclide angiography as methods of determining left ventricular ejection fraction. *J Nucl. Med.* 18: 600 1977.
- 18 Gorten, R., Hardy, L., McCraw, B., Stokes, J., Lomb, G.: The selective uptake of  $\text{Hg}^{203}$ -chlormerodrin in experimentally produced myocardial infarcts. *Amer Heart J* 72: 71 1966.
- 19 Hamilton, G., Trobaugh, G., Ritchie, J., William, D., Weaver, D., Gould, L.: Myocardial imaging with intravenously injected Thallium-201 in patients with suspected coronary artery disease. *Amer J Card.* 39: 347 1977.
- 20 Hemming, H., Scheffert, H., Ashburn, W., Kalliner, J.: Relation between left

sensitivity and specificity and rarely show false negative results. False positives appear in patients with unstable angina pectoris or with old infarcts, and this applies for both radionuclides. The decision about which radionuclide method or combination is most useful in the evaluation of a specific patient with chest pain largely depends on the clinical situation and the questions being asked. If an acute diagnosis is looked for  $^{99m}\text{Tc}$  pyrophosphate seems to be the isotope of choice, judging by the evidence in the literature (53-56). In a patient where all clinical evidence supports the diagnosis of myocardial infarction but where any of the laboratory parameters fail  $^{201}\text{Tl}$  seems to be the ideal isotope for the subacute situations. Several authors (54) recommend  $^{201}\text{Tl}$  when it is a question of silent and old infarction.

Any combination with radiocardiography seems to be feasible when the left ventricular function should be studied in a patient with or without an established acute myocardial infarction.

If any method, either positive or negative infarct scintigraphy yields a positive result, the probability that the patient has an acute infarction is more than 85 per cent. This at least equals the sensitivity of the otherwise routinely used clinical methods (20-22). The possibility of differentiating between unstable angina pectoris and myocardial infarction (29-56) adds another important dimension to these methods. Combined with radiocardiography and determination of left ventricular function it adds a new important, and powerful tool in the evaluation of patients with acute myocardial infarction.

Table II Summary of the result with  $^{99m}\text{Tc}$ -pyrophosphate

Number of patients	Diagnosis	Positive pyrophosphate scintigrams	Negative pyrophosphate scintigrams
188	Transmural AMI	180	8
5	Left Bundle Branch block with AMI	5	0
22	Subendocardial AMI	22	10
75	Unstable angina pectoris	52	23
29	Other cardiac disorders	5 (1 Chagas, 1 Prinzmetal, 2 ventricular aneurysms, 1 post defibrillation)	24
21	Non-cardiac disorders	0	21

## References

1. Abdulla, A., Canedo, M., Cortez, B., Mc Ginns, K., Wilhelm, S. Detection of unstable angina by  $^{99m}\text{Tc}$ -pyrophosphate myocardial scintigraphy. *Cher* ■ 168 1976
2. Ahmad, M., Dubiel, J., Verdon, T., Martin, R.: Technetium  $^{99m}$ -stannous pyrophosphate myocardial imaging in patients with and without left ventricular aneurysm. *Circulation* 53: 833 1976
3. Ashburn, B., Kossek, W., Harner, J., Peterson, K., Sobel, B. Left ventricular volume and ejection fraction determination by radioisotope angiography. *Semin. Nucl. Med.* 3 163 1973
4. Berger, H., Freedman, G., Zaret, B. Non invasive radioisotope imaging in the patient with cardiovascular disease. *Connecticut Medicine* 40 511 1976.
5. Berger, H., Gottschalk, A., Zaret, B. Radioisotope imaging of myocardial infarction in man. *J. Nucl. Med.* 18 594 1977
6. Bonte, F., Parkey, R., Graham, K., Stokley, E., Moore, J. A new method for radioisotope imaging of myocardial infarction. *Radiology* 110 473 1974
7. Borwink, E., Shames, D., Lippin, A., Tyberg, J., Townsend, R., Parmley, W. Non invasive quantification of myocardial infarction with Technetium- $^{99m}$  pyrophosphate. *Circulation* 52 909 1975
8. Boja, M., Parkey, R., Dea, J., Stokley, E., Harris, R., Bonte, P., Willerson, J.: Morphologic correlates of technetium  $^{99m}$  stannous pyrophosphate imaging of acute myocardial infarction in dogs. *Circulation* 52 596, 1975
9. Cabamon, J., Septfonds, J., Artus, J., Miro, L., Soucon, H.: Sémiologie scintigraphique de infarctus du myocarde. *J. de med. de Montpellier* 10 3 1973
10. Cairns, J., Fantus, I., Klassen, G.: Unstable angina pectoris. *Amer Heart J* 92 373 1976.
11. Carr, E., Benerwalter, W., Wegn, A., Bartlett, J. D.: Myocardial scanning with rubidium 86. *J. Nucl. Med.* 3 76, 1962.
12. Carr, E., Gleason, G., Shaw, J., Kroner, B. Direct diagnosis of myocardial infarction by photoscanning after administration of cesium — 131. *Amer Heart J* 68 627 1964
13. Coleman, E., Klem, M., Ahmed, A., Weiss, E., Buchholz, W., Sobel, B. Mechanisms contributing to myocardial accumulation of Technetium  $^{99m}$  Stannous pyrophosphate after coronary occlusion. *Amer J Card.* 39 85 1977
14. DiCola, V., Freedman, G., Downing, E., Zaret, B., Myocardial uptake of technetium  $^{99m}$  Stannous pyrophosphate following direct current trans-thoracic Counterschock. *Circulation* 54 982, 1976.
15. Duncan, B., Fulton, M., Morrison, S.C., Lutz, W., Donald, K., Kerr, F., Kirby, J., Julian, O., Oliver, M. Prognosis of new and worsening angina pectoris. *Brit. Med. J* 1 981 1976.
16. Eams, J., Walsh, M., Mahon, J. Value of Infarctspecifi. Isotope ( $^{99m}\text{Tc}$  labelled stannous pyrophosphate) in myocardial scanning. *Brit. Med. J* 11 517 1975
17. Folland, E., Ritchie, J., Hamilton, G., Kennedy, J. First pass and blood pool radioisotope angiography as methods of determining left ventricular ejection fraction. *J. Nucl. Med.* 18 600, 1977
18. Gerten, R., Hardy, L., McCraw, B., Stokes, J., Lomb, G. The selective uptake of  $\text{Hg}^{203}$ -chloromerodrin in experimentally produced myocardial infarction. *Amer Heart J* 72 71, 1966
19. Hamilton, G., Trobaugh, G., Ritchie, J., Williams, D., Warner, D., Gould, L. Myocardial imaging with intravenously injected Thallium-201 in patients with suspected coronary artery disease. *Amer J Card.* 39: 347 1977
20. Henning, H., Scheibert, H., Ashburn, W., Kalliner, J. Relation between left

sensitivity and specificity and rarely show false negative results. False positives appear in patients with unstable angina pectoris or with old infarcts, and thus applies for both radionuclides. The decision about which radionuclide method or combination is most useful in the evaluation of a specific patient with chest pain largely depends on the clinical situation and the questions being asked. If an acute diagnosis is looked for  $^{99m}\text{Tc}$  pyrophosphate seems to be the isotope of choice, judging by the evidence in the literature (53-56). In a patient where all clinical evidence supports the diagnosis of myocardial infarction but where any of the laboratory parameters fail  $^{201}\text{Tl}$  seems to be the ideal isotope for the subacute situations. Several authors (34) recommend  $^{201}\text{Tl}$  when it is a question of silent and old infarction.

Any combination with radiocardiography seems to be feasible when the left ventricular function should be studied in a patient with or without an established acute myocardial infarction.

If any method, either positive or negative infarct scintigraphy yields a positive result, the probability that the patient has an acute infarction is more than 85 per cent. This at least equals the sensitivity of the otherwise routinely used clinical methods (20, 22). The possibility of differentiating between unstable angina pectoris and myocardial infarction (29-56) adds another important dimension to these methods. Combined with radiocardiography and determination of left ventricular function it adds a new important, and powerful tool in the evaluation of patients with acute myocardial infarction.

Table II Summary of the result with  $^{99m}\text{Tc}$ -pyrophosphate

Number of patients	Diagnosis	Positive pyrophosphate scintigrams	Negative pyrophosphate scintigrams
188	Transmural AMI	180	8
5	Left Bundle Branch block with AMI	5	0
22	Subendocardial AMI	22	10
75	Unstable angina pectoris	52	23
29	Other cardiac disorders	5	24
		(1 Chagas, 1 Prinzmetal 2 ventricular aneurysms, 1 post defibrillation)	
21	Non-cardiac disorders	0	21

41. Platt, M., Mills, L., Parkey R., Wilkerson, J. Bonte, F. Shapiro, W. Slogg, W.: Perioperative myocardial infarction diagnosed by Technetium-99m stannous pyrophosphate myocardial scintigrams. *Circulation* 54: suppl III -24 1976.
42. Ramanathan, P. Genatra, R., Daulatram, K., Sen, P. Blau, M. Uptake of  $^{203}\text{Hg}$ -hydroxy-mercury-fluorescein in Myocardial infarcts. *J Nucl Med.* 12 641 1971
43. Rigo, P. Strauss, W. Tylor D. Kelly D. Wexfeldt, M., Pitt, B. Left ventricular function in acute myocardial infarction evaluated gated scintiphography. *Circulation* 50 678, 1974
44. Romhilt, D. Adolph, R., Sodd, V. Lemson, N., August, L., Nishiyama, A., Betke, R. Cerium-129 myocardial scintigraphy to detect myocardial infarction. *Circulation* 48 1242, 1973
45. Rose, L. Portability in nuclear medicine. *Applied Radiology* Nov Dec 210 1976.
46. Sapirstein, L. Regional blood flow by fractional distribution of indicators. *Amer J Physiol.* 193 161 1958
47. Schelbert, H., Henning, H., Ashburn, W. Verba, J. Karlner, J. O'Rourke, R. Serial measurements of left ventricular ejection fraction by radionuclide angiography early and late after myocardial infarction. *Amer J Card.* 38 407 1976.
48. Schelbert, H., Ingwall, J. Sybers, H., Ashburn, W. Uptake of infarct-imaging agents in reversibly and irreversibly injured myocardium in cultured fetal mouse heart. *Circ. Res.* 39 860, 1976.
49. Shen, A., Jennings, R. Myocardial calcium and magnesium in acute ischemic injury. *Amer J Pathol.* 67 417 1972.
50. Shen, A., Jennings, R. Kinetics of calcium accumulation in acute myocardial ischemic injury. *Amer J Path.* 67: 441 1972.
51. Strauss, W. Pitt, B.: Common procedures for noninvasive determination of regional myocardial perfusion, evaluation of regional wall motion and detection of acute infarction. *Am. J Card.* 38 731 1976.
52. Strauss, W. Pitt, B. Thallium-201 as a myocardial imaging agent. *Sem. Nucl. Med.* 7: 49 1977
53. Wackers, F. Koen, L., Sokole, E., Samson, G. v.d. Schoot, J. Wellens, A., Durrer D. Thallium-201 scintigraphy in unstable angina. *J Nucl. Med.* 18: 594 1977
54. Wackers, F. Sokole, E., Samson, G. v.d. Schoot, J. Wellens, H. Myocardial imaging in coronary heart disease with radionuclides with emphasis on Thallium 201. *Eur J Cardiol.* 4 273 1976.
55. Walsh, W. Schwartz, J. Bantovich, G. Booth, A., Harper P. Al-Sadir J. Resuekov L. Localization patterns of 99m Technetium-diphosphonate in experimental myocardial infarction. *Clin. Res.* 23 213 1975
56. Willerson, J. Parkey R., Bonte, F. Meyer S., Atkins, J. Seckley E. Technetium stannous pyrophosphate myocardial scintigrams in patients with chest pain of varying etiology. *Circulation* 51 1046, 1975
57. Zaret, B. Vlay S. Freedman, G. Wollson, S., Cohen, L. Quantitative relationship between Potassium-43 imaging and left ventricular cineangiography following myocardial infarction in man. *Circulation* 52 1076, 1975

- ventricular performance assessed by scintigraphic and enzymatic methods. *J Nucl Med* 18 681 1977
- 21 Henning R., Lundman, T Swedish cooperative CCU-study *Acta Med. Scand suppl* 586 1975
- 22 Holman, L., Chisholm, R., Braunwald, E. The prognostic implication of acute myocardial infarct scintigraphy *J Nucl Med.* 18 611 1977
- 23 Holman, B., Davis, M., Hanson, R. Myocardial infarct imaging with Technetium labelled complexes. *Sem. Nucl Med.* 7 29 1977
- 24 Holman L., Lesch, M., Zweiman, F., Tenite, J., Lown, B., Gorlin, R. Detection and sizing of acute myocardial infarcts with  $^{99m}\text{Tc}$  tetracycline. *New Engl. J of Med* 291 159 1974
- 25 Hubner P. Radioisotopic detection of experimental myocardial infarction using mercury derivatives of fluorescein *Cardiovasc. Res.* 4 509 1970
- 26 Jacobstein, J., Alonso D., Roberts, A., Cipriano, P., Combes, J., Post, M. Early diagnosis of myocardial infarction in the dog with  $^{99m}\text{Tc}$ -Glucosephotonate *J Nucl Med.* 18 413 1977
- 27 Leibowitz, A., Greene, M. Fairchild, R., Bradley Moore, P., Atkins, H., Anson, A., Richards, P., Belgrave, E. Thallium 201 for medical use. *J Nucl. Med.* 16 151 1975
- 28 Lessem, J. Johansson, B W Nosslin, B. Myocardial scintigraphy in 150 coronary care unit patients. *European J Cardiol* 4 453 1976
- 29 Lessem, J., Johansson, B W., Nosslin, B., Thorell, J. Clinical analysis of myocardial scintigraphy with  $^{99m}\text{Tc}$  pyrophosphate Medical Radionuclide imaging Proceedings of a symposium vol II 231 1977 IAEA, Vienna.
- 30 Lessem J. Persson, B: Myocardial scintigraphy in Chagas disease. *Lancet*, in press, 1977
- 31 Lessem, J. Poliment, P. Page, E., Resnekov L., Harper P.  $\text{Tc } 99\text{m}$  pyrophosphate image of rat ventricular infarcts, correlation of time course with microscopic pathology *Amer J Card.* 39 279 1977
- 32 Lyons, K., Olson, H. Kupers, J. Aronow W., Stemmer, E. Preoperative, postoperative and late follow-up  $\text{Tc } 99\text{m}$  pyrophosphate myocardial scintigraphy and coronary by pass surgery *J Nucl Med.* 18; 612, 1977
- 33 Malek, P., Vavrejn, B., Ratsky J. Konrad, L., Kolc, J. Detection of myocardial infarction by in vivo scanning. *Cardiologia* 51 22, 1967
- 34 Maseri, A., Parodi, O. Severi, S., Desola, A. Transient transmural reduction of myocardial blood flow demonstrated by Thallium 201-scintigraphy as a cause of variant angina. *Circulation* 54 280 1976
- 35 Mc Laughlin, P. Coates, G., Wood, D. Craddock T., Morch, J: Detection of acute myocardial infarction by Technetium  $99\text{m}$  polyphosphate. *Amer J Cardiol* 33 390 1975
- 36 Oldendorf W. Evaluation of a simple technique for abrupt intravenous injection of radioisotope. *J Nucl. Med* 6 205 1965
- 37 Parusi, A., Tow O., Sasakala, A. Clinical appraisal of current nuclear and other noninvasive cardiac techniques. *Am J Card.* 38 722, 1976
- 38 Parkey R., Bonte F. Stokely E., Lewis, S. Graham, K., Buja, M. Willerson, J. Acute Myocardial Infarction imaged with  $^{99m}\text{Tc}$  stannous pyrophosphate and  $^{201}\text{Tl}$  a clinical evaluation. *J Nucl Med.* 17: 776, 1976
- 39 Pitt, B., Strauss, W: Myocardial imaging in the Noninvasive evaluation of Patients with suspected ischemic heart Disease. *Amer J Cardiol* 37 797 1976
- 40 Pitt, B., Strauss, W. Myocardial Perfusion Imaging and gated cardiac blood pool scanning *Amer J Card* 38: 739 1976

Renal tubular resorption and storage of myoglobin have been documented (3, 2). With increasing plasma levels, tubular resorption of myoglobin also increases. Probably only when this absorptive capacity ( $T_m$ ) is exceeded will myoglobin appear in urine. Thus, free myoglobin might be handled by the nephron in a manner similar to glucose, phosphate, uric acid, hemoglobin, amino acids, and other proteins (4). The catabolism of myoglobin in the body is similar to that of hemoglobin. Bywaters (6) observed by peribulburemia in man in clinical states of muscle damage and myoglobinuria. The fate of the globin portion is not known. Probably cathepsinlike proteolytic factors are involved. Kagen and Gurevich (12) found these properties in tissue extracts: cardiac muscle, liver, spleen, and urine. Under acid conditions in the presence of these extracts, myoglobin lost its antigenic properties. Moreover, the kidney might be important in the breakdown of proteins small enough to be filtered (5).

#### *Laboratory aids in diagnosing myoglobinemia and myoglobinuria*

The diagnosis of myoglobinuria and/or myoglobinemia has in the past been regarded as difficult. The first step toward identification of myoglobin in a sample of urine is usually to test for "occult blood" with an assay that relies upon the enzymatic property of myoglobin to release oxygen from hydrogen peroxide. A dye such as toluidine, which develops color in the presence of oxygen, makes this reaction easily perceptible. This test is sensitive and can detect 5 to 10  $\mu\text{g}$  per ml, and in certain urines, even smaller amounts. By using a test paper technique for estimating small amounts of urinary glucose (28) Urning *et al* (31, 32) succeeded in making the peroxidase test still more sensitive — less than 1  $\mu\text{g}/\text{ml}$ . However, all tests based on the peroxidase activity of myoglobin lack specificity for myoglobin; they will react also for hemoglobin.

Electrophoresis on a variety of supporting media (paper, urea, cell loss acetate, acrylamide gel), precipitation methods with

ammonium sulfate, spectrophotometry and isoelectric focusing are techniques difficult to interpret in the presence of denatured protein.

Immunological methods have been the most sensitive and precise. Specific antisera, which do not react detectably with hemoglobin or other constituents of serum, urine, or muscle tissue, allow detection of myoglobin at a level of sensitivity greater than with other techniques. Precipitation methods permit detection of 5 to 10  $\mu\text{g}$  per ml; complement fixation and hemagglutination methods increase the sensitivity to 1  $\mu\text{g}/\text{ml}$ . The use of  $^{125}\text{I}$  myoglobin and anti-human myoglobin in a radioimmunoassay allows 0.5  $\text{ng}$  of myoglobin to be determined. However, even if highly sensitive methods are used for the detection of myoglobin in serum or urine, care must be exercised in the interpretation in view of the above-mentioned chemical, physiological, and metabolic factors affecting myoglobin.

#### *Myoglobinuria and myoglobinemia in myocardial infarction*

Myoglobinuria is generally considered uncommon, although it has been reported in a wide variety of clinical conditions (26). In 1936, Kim and Reinhart (15) were the first to find myoglobin in serum and urine of patients after myocardial infarction. Highest levels were noted in the first days of illness. They used a complicated precipitation technique with ammonium.

Despite immunological methods for the determination of myoglobin having been available since 1928, it is only during the last 10 years that they have been developed for differentiating myoglobin from hemoglobin. In 1966, Srauzer *et al* (30), using antibody precipitation techniques, detected myoglobin in the urine of patients after myocardial infarction. Due to the lack of specificity the test was forgotten, and the question of myoglobinuria as an aid in the diagnosis of myocardial infarction remained open until 1970, when Adams and Elliot (1) reported myoglobinuria after cardiac infarction. They used a qualitative hemagglutina-



# Myoglobin

Bengt Scherstén, Dag Ursing and  
Gunnel Jonsson

Dept. of Internal Medicine University Hospital of Lund LUND  
and the Unit for Community Care Sciences  
DALBY SWEDEN

In 1897 Mörner (21) prepared the muscle pigment from dogs. In a classical study he demonstrated spectrophotometric differences between the pigment and hemoglobin and suggested a new name for it myoglobin.

In clinical medicine, it is important to know whether or not myoglobin is released into the circulation as a result of infarction of heart muscle. The recognition of myoglobinemia and/or myoglobinuria might be of diagnostic and prognostic importance, as the amount of myoglobin released should indicate the extent and severity of muscle damage (13). Substantial evidence suggests that damage to the cardiac muscle mass causes the release of various intracellular enzymes into the circulation. The importance of determination of serum enzyme activity profiles of ASAT, ALAT, LD-isoenzymes is well documented. A promising approach is the quantification of creatine phosphokinase (CK) by measurement either of total enzyme activity (25) or of the activity of its cardiac-specific fraction CK-MB. A similar high degree of specificity has been attributed to arginase (23) and glycogen phosphorylase (16) in the early differential diagnosis of myocardial infarction. Determination of serum adenylate kinase activity (8) seems to offer interesting prospects in the early diagnosis of myocardial infarction.

It seems worth while to encourage all studies directed toward new diagnostic procedures that can help us to improve our diag-

nostic acumen in acute myocardial infarction and ultimately to indicate the extent of the injury. Prognostic indices should in future include some measurement of infarct size (17).

## *Some chemical, physiological, and metabolic aspects of myoglobin*

Hagen and Gurevich (11) showed that myoglobin was localized to three regions in the muscle cell: transverse striations of the contractile elements, sarcolemmal regions, and intracellular membranes of fibrillar structures. Myoglobin has a molecular weight of approximately 17 000 daltons.

When released from muscle at injury or disease, myoglobin can enter the circulation and from there be cleared by renal mechanisms. Haptoglobin does not bind human myoglobin (9). Latham (18) studying canine myoglobin, found significant binding of this protein by canine plasma. The maximum binding averaged 21 mg per 100 ml of plasma. At concentrations of myoglobin in plasma below this value, approximately 15 to 50 per cent of the myoglobin in plasma was in the unbound state. The myoglobin-binding protein appeared to be either an  $\alpha_2$  or a  $\beta$ -globulin.

In man the effective renal threshold is not known, nor is it known how important a role the plasma capacity plays in binding myoglobin in the prevention of renal excretion.

Renal tubular reabsorption and storage of myoglobin have been documented (3-2). With increasing plasma levels, tubular reabsorption of myoglobin also increases. Probably only when this absorptive capacity ( $T_m$ ) is exceeded will myoglobin appear in urine. Thus, free myoglobin might be handled by the nephron in a manner similar to glucose, phosphate, uric acid, hemoglobin, amino acids, and other proteins (4). The catabolism of myoglobin in the body is similar to that of hemoglobin. Bywaters (6) observed by perbilirubinemia in man in clinical states of muscle damage and myoglobinuria. The fate of the globin portion is not known. Probably cathepsinlike proteolytic factors are involved. Kagen and Gorevich (12) found these properties in tissue extracts, cardiac muscle, liver, spleen, and urine. Under acid conditions in the presence of these extracts, myoglobin lost its antigenic properties. Moreover the kidney might be important in the breakdown of proteins small enough to be filtered (3).

#### *Laboratory aids in diagnosing myoglobinemia and myoglobinuria*

The diagnosis of myoglobinemia and/or myoglobinuria has in the past been regarded as difficult. The first step toward identification of myoglobin in a sample of urine is usually to test for "occult blood" with an assay that relies upon the enzymatic property of myoglobin to release oxygen from hydrogen peroxide. A dye such as toluidine, which develops color in the presence of oxygen, makes this reaction easily perceptible. This test is sensitive and can detect 5 to 10  $\mu\text{g}$  per ml, and in certain urines, even smaller amounts. By using test paper technique for estimating small amounts of urinary glucose (28) Ursing *et al* (31-32) succeeded in making the peroxidase test still more sensitive—less than 1  $\mu\text{g}/\text{ml}$ . However all tests based on the peroxidase activity of myoglobin lack specificity for myoglobin; they will react also for hemoglobin. Electrophoresis on a variety of supporting media (paper, starch, cellulose acetate, acrylamide gel), precipitation methods with

ammonium sulfate, spectrophotometry and isoelectric focusing are techniques difficult to interpret in the presence of denatured protein.

Immunological methods have been the most sensitive and precise. Specific antisera which do not react detectably with hemoglobin or other constituents of serum, urine, or muscle tissue, allow detection of myoglobin at a level of sensitivity greater than with other techniques. Precipitin methods permit detection of 5 to 10  $\mu\text{g}$  per ml; complement fixation and hemagglutination methods increase the sensitivity to 1  $\mu\text{g}/\text{ml}$ . The use of  $^{125}\text{I}$  myoglobin and anti-human myoglobin in radioimmunoassay allows 0.5 ng of myoglobin to be determined. However even if highly sensitive methods are used for the detection of myoglobin in serum or urine, care must be exercised in the interpretation in view of the above-mentioned chemical, physiological, and metabolic factors affecting myoglobin.

#### *Myoglobinemia and myoglobinuria in myocardial infarction*

Myoglobinuria is generally considered uncommon, although it has been reported in a wide variety of clinical conditions (26). In 1956, Kim and Reinhart (15) were the first to find myoglobin in serum and urine of patients after myocardial infarction. Highest levels were noted in the first days of illness. They used a complicated precipitation technique with ammonium.

Despite immunological methods for the determination of myoglobin having been available since 1928, it is only during the last 10 years that they have been developed for differentiating myoglobin from hemoglobin. In 1966, Strauser *et al* (30), using antibody precipitation techniques, detected myoglobin in the urine of patients after myocardial infarction. Due to the lack of specificity the test was forgotten, and the question of myoglobinuria as an aid in the diagnosis of myocardial infarction remained open until 1970, when Adams and Elliot (1) reported myoglobinuria after cardiac infarction. They used qualitative hemagglutina-

nation inhibition test. Myoglobinuria was detected in 35 of 44 patients after myocardial infarction. However the specificity of this test was considered low as the tests were positive five times when no diagnosis of myocardial infarction was made.

Levine *et al* (19) used the same technique with an estimated sensitivity between 0.6 and 2.0  $\mu\text{g}$  of myoglobin per ml of urine. Myoglobinuria was detected at least once during the illness in 92 per cent of the patients. On day one, the myoglobin test was positive in 88 per cent, on day two, in 87 per cent, and on day three, in 76 per cent.

The radial immunodiffusion assay described by Saranchack and Bernstein (27) is an example of differences in the sensitivity for myoglobin in urine of the immunological techniques. They found significant levels of myoglobin at or above 50  $\mu\text{g}/\text{ml}$  in urine samples from 59 of 60 patients with myocardial infarction. Volk *et al* (33) studied myoglobin in serum by an immunological method using the technique according to Ouchterlony with a sensitivity of 15  $\mu\text{g}/\text{ml}$ . Myoglobin was released into serum in the first 30 minutes after the attack of pain. There was a distinct difference in titre between survivors and those who died. They interpreted the influx of myoglobin to be a sequela to cardiogenic shock and hypoxemia. Therefore myoglobin is not found in sudden death.

Since 1973 several reports have been published (20, 22, 10, 24, 34) where serum myoglobin levels have been measured by means of radioimmunoassay capable of detecting nanograms of myoglobin per ml of serum. With these methods, myoglobin has been identified in sera from normal adults; it ranged from 5 to 85 ng/ml. Raised myoglobin levels were present in all except two of 99 cases reported in total. Stone *et al* (29) found a mean serum concentration of 528  $\pm$  76 ng/ml. They further report that only two of another 44 patients admitted with chest pain but without subsequent electrocardiographic, enzymatic, or technetium-99m stannous pyrophosphate myocardial

scintigraphic evidence of acute myocardial infarction had raised myoglobin levels; the mean value for this group was within the normal range ( $44 \pm 11$  ng/ml).

Willerson *et al* (34) studied the relation between the histological infarct size in dogs and peak myoglobin serum levels and found a highly significant correlation ( $r = 0.83$ ,  $p < 0.01$ ). The serum myoglobin levels began to rise within two hours and peaked in six hours after experimentally induced acute myocardial infarction.

Kagen *et al* (14) and Donald *et al* (7) found that urinary myoglobin levels, when measured simultaneously with serum, did not correlate well with the marked temporal changes that occurred in the serum. The variable myoglobin excretion pattern suggests that, in seemingly uncomplicated myocardial infarction, there is considerable variation between patients in the pattern of evolution of the infarction process.

#### Concluding remarks

The conclusion is that transient myoglobinemia seems to be one of the earliest laboratory abnormalities occurring in myocardial infarction; therefore it should prove useful as a diagnostic aid in patients. Further studies are necessary regarding the prognostic value of myoglobinemia. Both chemical and immunological methods for demonstrating myoglobinuria require better documentation of their sensitivity before the value of detecting myoglobin in urine as a tool for diagnosing myocardial infarction can be determined.

#### References

1. Adams, E. C., Jr & Elliot, T. A. Urinary myoglobin in myocardial infarction. *JAMA* 211 1013 1970.
2. Andersson, W. A. The use of exogenous myoglobin as an ultrastructural tracer. Reabsorption and translocation of protein by the renal tubule. *J. Histochem. Cytochem.* 0 672, 1974.

- 3 Blöthner A., Karaniky K P Metz, J & Tangreter R.: Zum Schicksal, vor allem zur Nierenausscheidung von exogenem Hämoglobin und Myoglobin bei der Ratte. *Z. Ges. Exp. Med.* 155:112, 1971
- 4 Bunn, H. F Esham, W T & Bull, R. W The renal handling of hemoglobin. I. Glomerular filtration. *J Exp. Med.* 129:909 1969
- 5 Bunn, H. F Esham, W T & Bull, R. W The renal handling of hemoglobin. II. Carabohem. *J Exp. Med.* 129:925 1969
- 6 Bywaters, E. G L: Myoglobin and myoglobinemia in the muscle. Edited by M. Polonovski. L'Expansion, Paris. 1952, p. 213
- 7 Donald, T G., Cloonan, M. J Neale, C., & Wilken, D E. L. Excretion of myoglobin in urine after acute myocardial infarction. *Brit. Heart J* 39:29 1977
- 8 Fridtz, G Ericson, P & Ronquist, G Serum adenylate kinase activity in the early phase of acute myocardial infarction. Uppsala. *J Med. Sci.* 81 155 1976.
- 9 J vid, J Fischer D S & Spaet, T H. Instability of heptoglobin to band hemoglobin. *Blood* 14:683 1959
- 10 Jetty R. V Nevaz, G. W Palmer F J Nelson, J C. Radioimmunoassay of serum myoglobin in acute myocardial infarction. *Am. J Card.* 33 147 1975
- 11 Kagen, L. J & Gurevich, R. Localization of myoglobin in human skeletal muscle using fluorescent antibody technique. *J Histochem. Cytochem.* 15 436, 1967
- 12 Kagen, L. J & Gurevich, R. "Myoglobolytic" activity of human skeletal muscle and other tissues. *Proc. Soc. Exp. Biol. Med.* 130:923, 1969
- 13 Kagen, L. J Myoglobin. Biochemical, physiological and clinical aspects. Columbia University Press, New York and London, 1973 p. 93
- 14 Kagen, L. J Scheidt, S., Roberts, L., Porter A., & Paul, H. Myoglobinemia following acute myocardial infarction. *JAMA* 58 177 1975
- 15 Kra, A. & Rembart, N Über den nachweis der Myoglobin in Serum und im Harn nach Herzinfarkt. *Wien. Klin. Wochr* 68:154 1956.
- 16 Krons, E. G., Böhm, M., Will, H. & Wollenberger A. Glykogenphosphorylase b ein neuer Serumentzymtest für den Herzinfarkt. *Dtsch Gesundheitsw* 27:903 1972.
- 17 Lancet: Prognosis in myocardial infarction. *Lancet* 1:179 1977
- 18 Latham, W The binding of myoglobin by plasma protein. *J Exp Med.* 111: 65 1960.
- 19 Levine, R. S Alterman, M., Gubner R. S. & Adams, E. C., Jr: Myoglobinuria in myocardial infarction. *Am. J Med. Sci.* 162:179 1971
- 20 Lwibanga Mekasa, J S., Libby P Bloor C. M., & Maroko, P R. The serum myoglobin following experimental coronary occlusion. *Circulation, Suppl. IV VII—VIII, IV—129* 1973.
- 21 Möhrner K.A.H. Beobachtungen über den Muskelfarbstoff. *Nord. Med. Arhiv* 30 1 1897
- 22 Palmer F J Nevaz, G W Stuart, C. G Lewis, J E., Jetty R. V & Nelson, J C. A radioimmunoassay for myoglobin. *Circulation, Suppl. III, 49—50* 111—197 1974
- 23 Porombaka, Z. & Kedra, M. Early diagnosis of myocardial infarction by arginase activity determination. *Clin. Chem. Acta* 60:335 1975
- 24 Reschlin, M., Visco, J P & Klocke, F J Serum Myoglobin in myocardial infarction. Results with radioimmunoassay. *Clin. Res.* 24:421 A, 1976.
- 25 Roberts, R., Gowda, K. S., Ledbrook, P A., & Sobel, B. E. Specificity of elevated serum MB creatine phosphokinase activity in the diagnosis of acute myocardial infarction. *Am. J Cardiol.* 36:433 1975

nation inhibition test Myoglobinuria was detected in 35 of 44 patients after myocardial infarction. However the specificity of this test was considered low as the tests were positive five times when no diagnosis of myocardial infarction was made.

Levine *et al* (19) used the same technique with an estimated sensitivity between 0.6 and 2.0  $\mu\text{g}$  of myoglobin per ml of urine. Myoglobinuria was detected at least once during the illness in 92 per cent of the patients. On day one, the myoglobin test was positive in 89 per cent, on day two, in 87 per cent, and on day three, in 76 per cent.

The radial immunodiffusion assay described by Saranchack and Bernstein (27) is an example of differences in the sensitivity for myoglobin in urine of the immunological techniques. They found significant levels of myoglobin at or above 50  $\mu\text{g}/\text{ml}$  in urine samples from 59 of 60 patients with myocardial infarction Volk *et al.* (33) studied myoglobin in serum by an immunological method using the technique according to Ouchterlony with a sensitivity of 15  $\mu\text{g}/\text{ml}$ . Myoglobin was released into serum in the first 30 minutes after the attack of pain. There was a distinct difference in titre between survivors and those who died. They interpreted the influx of myoglobin to be a sequela to cardiogenic shock and hypoxemia. Therefore myoglobin is not found in sudden death.

Since 1973 several reports have been published (20, 22, 10, 24, 34) where serum myoglobin levels have been measured by means of radioimmunoassay capable of detecting nanograms of myoglobin per ml of serum. With these methods, myoglobin has been identified in sera from normal adults it ranged from 6 to 85 ng/ml. Raised myoglobin levels were present in all except two of 99 cases reported in total Stone *et al* (29) found a mean serum concentration of  $528 \pm 76$  ng/ml. They further report that only two of the remaining 44 patients admitted with chest pain but without subsequent electrocardiographic, enzymatic, or technetium-99m stannous pyrophosphate myocardial

scintigraphic evidence of acute myocardial infarction had raised myoglobin levels the mean value for this group was within the normal range ( $44 \pm 8$  ng/ml).

Willerson *et al* (34) studied the relation between the histological infarct size in dogs and peak myoglobin serum levels and found a highly significant correlation ( $r = 0.83$ ,  $p < 0.01$ ). The serum myoglobin levels began to rise within two hours and peaked in six hours after experimentally induced acute myocardial infarction.

Kagen *et al* (14) and Donald *et al* (7) found that urinary myoglobin levels, when measured simultaneously with serum, did not correlate well with the marked temporal changes that occurred in the serum. The variable myoglobin excretion pattern suggests that, in seemingly uncomplicated myocardial infarction, there is considerable variation between patients in the pattern of evolution of the infarction process.

#### Concluding remarks

The conclusion is that transient myoglobinemia seems to be one of the earliest laboratory abnormalities occurring in myocardial infarction therefore it should prove useful as a diagnostic aid in patients. Further studies are necessary regarding the prognostic value of myoglobinemia. Both chemical and immunological methods for demonstrating myoglobinuria require better documentation of their sensitivity before the value of detecting myoglobin in urine as a tool for diagnosing myocardial infarction can be determined.

#### References

1. Adams, E. C., Jr & Elliot, T. A. Urinary myoglobin in myocardial infarction. *JAMA* 211: 1013, 1970.
2. Andersson, W. A. The use of exogenous myoglobin as an ultrastructural tracer. Reabsorption and translocation of protein by the renal tubule. *J. Histochem. Cytochem.* 20: 67, 1972.

# Morphological diagnosis of early acute myocardial infarction

Nils H Sternby

Dept. of Pathology General Hospital MALMÖ SWEDEN

In recent years, much work has been done to find reliable morphological methods for diagnosing early myocardial infarction (1). The lack of them makes it impossible to compare the reliability of different clinical methods and creates difficulties in finding the mechanisms of death due to acute heart failure. Think of the discussions on the relation of coronary thrombosis to myocardial infarction! Patients dying shortly after a suspected infarction often show no coronary thrombosis, but such cases could well be due to heart failure of noninfarction type and thus would not show any thrombosis.

Many methods are available for use by morphologists (Table 1). They can be divided into macro- and microscopical. There are also methods that use chemical analysis and the recently introduced methods that employ radioactive isotopes. However not only the myocardium should be studied, also lesions of the coronary arteries are of prime importance. We look for fresh thrombi or other type of coronary occlusion. For instance hemorrhage in an atherosclerotic plaque or embolus, or perhaps only atherosclerosis with varying degree of stenosis. For judging coronary stenosis, post-mortem angiography is of value, especially in subjects with extensive calcifications. The disadvantage of such angiography is that it makes it more difficult or impossible to use other diagnostic methods, for instance chemical analysis or enzyme histochemistry.

The macroscopical changes of early infarction are pallor and softening corresponding to oedema. Most text-books state that myocardial infarction is detectable first after 12–18 hours, and this seems to be correct, although some pathologists claim to be able to diagnose an infarction macroscopically already after 4–6 hours. The macroscopical diagnosis can be improved by, for instance, enzyme- and fluorescence stainings. The most used enzymatic method is based on the loss of dehydrogenase activity in ischaemic myocardium. This is shown by treating the myocardium with tetrazolium derivatives, usually so-called nitro-BT (2). With this method, which is resistant against autolysis, myocardial infarcts can be diagnosed within 6–8 hours.

A further macroscopical method is fluorescence studies of the myocardium after intravenous administration of tetracycline compounds (3). In early stages, the infarcted area does not show any fluorescence after 1–2 hours, the fluorescence is concentrated to the zone between normal and ischaemic myocardium. This zonal fluorescence is stable in contrast to the one in the normal myocardium. In later stages, the tetracycline derivatives are concentrated in the necrotic myocardium, which is then clearly demarcated. This method has mainly been used experimentally but it seems to be worth another clinical trial.

Regarding light microscopic diagnosis on

- 26 Rowland, L.P. & Penn, A.S. Myoglobinuria. *Med. Clin N Am.* 56:1233 1972
- 27 Saranchak, H. J. & Bernstein S. H. A new diagnostic test for acute myocardial infarction. The detection of myoglobinuria by radioimmunodiffusion assay. *JAMA* 228:1251 1974
- 28 Scherstén, B., Dahlqvist, A., Fritz, H., Köhler, L., & Westlund, L.: Screening for bacteriuria with a test paper for glucose. *JAMA* 204:205 1968
- 29 Stone, M. J., Waterman, M. R., Harimoto, D., Murray G., Willson, N., Platt, M. R., Blomqvist, G., & Willerson, J. T.: Serum myoglobin level as diagnostic test in patients with acute myocardial infarction. *Brit. Heart J* 39:375 1977
- 30 Strausser H. R., Rothfeld, E. L., & Bucu, R. A. Isolation and preservation of human myoglobin for use in immunologic detection of myoglobinuria. *Proc. Soc. Exp Biol Med* 122:621 1966
- 31 Ursing D., Jonsson, G. Lundquist, I. & Scherstén, B. Myoglobinnivåer i urin vid hjärtinfarkt. *Hygiea* 84:146, 1975
- 32 Ursing, D., Lundquist, I. Scherstén, B. & Westlund, L. Snabbdiagnostik av hjärtinfarkt med papperstest för påvisande av myoglobin i urin. *Hygiea* 84:146, 1975
- 33 Volk P. Fritschen U., & Begemann, M. Myoglobin in Serum nach Herzinfarkt. *Münch. Med. Wschr* 115:2122, 1973
- 34 Willerson J. T. Polner L., Buja, L. M., Waterman, M.R., Gomez Sanchez, C.L., Templeton, G.H., & Stone, M.J.: Myoglobinemia as a clue to the presence of acute myocardial infarction. *Clin. Res* 24:422 A, 1976

activity in the myocardium changes. Dehydrogenases of different types diminish in activity as do alkaline phosphatases and phosphokinases. Dehydrogenases are mostly used for this type of studies. Opinions vary about what type of enzyme is most suitable to study. Succinyldehydrogenase is studied with the previously mentioned nitro-BT method (2). Other authors have used malate-dehydrogenase, or butyrate-dehydrogenase. Although there is some disagreement about how autolysis affects these methods, it seems evident that some of them can be used also several days after death. The same seems valid for estimates of creatinephosphokinase activity.

Could we use electron microscopy to show early myocardial ischaemia? It is well known that morphological changes occur within 15 minutes after ischaemia and are well developed after about 30–60 minutes. The changes are the same as those caused by autolysis, and this makes such a method practically unusable. But it is possible to use it in experimental work.

Chemical analysis has been shown to be a reliable sign of ischaemic damage (15). Within 10–15 minutes after ischaemia, the amount of sodium is increased in the infarcted area, and potassium is lost. Also concentration of other ions, for instance magnesium and calcium, is changed. Most studies have used the potassium-sodium ratio, which decreases in ischaemic myocardium compared with normal myocardium. The estimate is independent of autolysis, and the method seems to be reliable. The disadvantage is that several parts of the myocardium must be studied and that localization and quantitation of myocardial damage is difficult.

In recent years, the use of radioactive isotopes for detecting myocardial ischaemia, both clinically and morphologically, has become popular (16, 17). Mainly two methods can be used either positive in which isotopes are concentrated in the necrotic myocardium, or negative where isotopes are concentrated in the normal myocardium but not in the infarction. Examples

of the latter type of isotopes are potassium and its analogues rubidium, cesium, and thallium. Of isotopes concentrating in the infarcted myocardium, the prototypes are tetracyclines and principally technetium-labelled stannum-pyrophosphate. Both types of isotope-diagnostic methods are used to show myocardial infarction clinically. Morphological studies have shown that these methods are reliable for both quantitative and topographic assessments.

What methods are then of practical use for diagnosis of early myocardial infarction? Ordinary light microscopy cannot positively diagnose an infarction that is younger than about 8 hours. By using tetrastannum technique, this period can be shortened by about 2 hours. A very reliable but more elaborate method is to study the potassium-sodium ratio in the myocardium, the time then being reduced to 1–2 hours. During the first three hours, different enzyme histochemical methods can be employed but autolysis might affect them. Fluorescent methods are of use within the first hours, but for the diagnosis of a recent infarction, tetracycline derivatives should probably be used. If isotopes are given as soon as possible, study of their distribution within the myocardium will be of great value. These methods cannot be applied to all instances of sudden heart death which occur outside the hospital. They are also difficult to apply to deaths within the hospital unless special arrangements are made to perform a post mortem soon after death. In such cases, there does not seem to be any better method than chemical determination during the first three hours after a suspected myocardial infarction. During the next three hours, fluorescent and some enzyme histochemical methods can also be used.

## Morphological diagnosis of early myocardial infarction

### Coronary arteries

#### Macroscopical methods

Without aid

With aid



routine (hematoxylin-eosin) stained slides, the criteria laid down by Mallory and co-workers (4) and Lodge-Patch (5) are still used. The earliest change is oedema, which is noticeable after about 2 hours. Four hours after the infarction the cell nuclei begins to become pyknotic and after about 6 hours, changes of the cytoplasm begin to appear i.e. increased eosinophilia, shrinking, and loss of cross striation. Infiltration of polymorph-nuclear leukocytes begins about now and this change seems to be one of the best signs of an infarction, as the other changes are identical with those appearing during autolysis. The leukocyte infiltration reaches its maximum after about 24 hours and persists for another one or two days and then slowly disappears. At the end of the first week, pigment filled macrophages appear together with lymphocytes and plasma-cells and fibro-blast proliferation. Later eosinophilic leukocytes might appear and collagen material is laid down. Proliferation of thin walled blood vessels begins at the end of the first week and reaches its maximum after about 4 weeks. All these changes are most pronounced in the edges of the infarction. In dating the age of an infarct, it is important to take the size of the necrosis into account.

A further histological method was published in 1972 by Bouchardy and Majno (6). According to them, it is always possible to find especially at the edge of an infarction, myocardial fibres that are stretched thin, and wavy. This change is said to appear very quickly certainly within an hour and possibly as early as two minutes after the infarction. But most pathologists seem very sceptical about this observation and other studies have not supported the method. None the less, several papers state that no such changes were found in recent myocardial infarction.

Several methods are published about light microscopic diagnosis on specially stained slides. PAS-staining was previously used, as a diastase-resistant mucus protein appears in the necrotic muscle cell. This is not apparent until the infarction is visible in also routine-

stained specimens, and the method is thus useless for early diagnosis. Another more promising method is the PTAH-staining, which is said to be able to delineate rather early ischaemic lesions. With a standardized and carefully worked out technique, this method, dealt with in detail by Professor Voigt, is of great help and seems to reveal recent infarctions.

Poley and coworkers (1) introduced a further special method in 1964 based on the observation by Selye (8) that myocardial fibres experimentally damaged by various toxins, showed eosinophilia when stained with acid fuchsin. Poley noted that this method was somewhat unreliable, but it was re-introduced by Lie (9) with the statement that this fuchsinophilia was a very good indication of myocardial ischaemia. This is certainly not our experience or that of others (10). Lie and coworkers (11) 1971 introduced the so-called MBFP (hematoxylin basic fuchsin-picric acid) staining which was said to be much more reliable and to be able to diagnose infarctions only a few hours old. Positive staining reactions were even reported already after 30 minutes. This positive staining, the so called fuchsinorrhagia, has been much criticised as most unreliable. Although papers exist in favour of this method (12) most authors deny its value (10, 13).

Fluorescence methods can also be used histologically. The previously mentioned tetracycline method (3) gives fluorescence on both fresh sections and formalin-fixed/paraffin embedded slides. Other methods that seem promising but which have been used experimentally are acridine-orange and astraphosphine staining the latter for showing accumulation of fat (14). Acridine-orange staining, which can be used on both fresh and formalin fixed material, shows ischaemic damage after about 3 hours on fresh myocardium and after about 5 hours on fixed material.

Several enzyme histochemical methods for the detection of early myocardial ischaemia have been described. It is well known that, soon after ischaemia, enzyme

activity in the myocardium changes: dehydrogenases of different types diminish in activity as do alkaline phosphatases and phosphokinases. Dehydrogenases are mostly used for this type of studies. Opinions vary about what type of enzyme is most suitable to study Succinyldehydrogenases are studied with the previously mentioned nitro-BT method (2). Other authors have used malate-dehydrogenases, or butyrate-dehydrogenase. Although there is some disagreement about how autolysis affects these methods, it seems evident that some of them can be used also several days after death. The same seems also for estimates of creatinphosphokinase activity.

Could we use electron-microscopy to show early myocardial ischaemia. It is well known that morphological changes occur within 15 minutes after ischaemia and are well developed after about 30—60 minutes. The changes are the same as those caused by autolysis, and thus makes such method practically unusable. But it is possible to use it in experimental work.

Chemical analysis has been shown to be reliable sign of ischaemic damage (15). Within 10—15 minutes after ischaemia, the amount of sodium is increased in the infarcted area, and potassium is lost. Also concentration of other ions, for instance magnesium and calcium, is changed. Most studies have used the potassium-sodium ratio, which decreases in ischaemic myocardium compared with normal myocardium. The estimate is independent of autolysis, and the method seems to be reliable. The disadvantage is that several parts of the myocardium must be studied and that localization and quantitation of myocardial damage is difficult.

In recent years, the use of radioactive isotopes for detecting myocardial ischaemia, both clinically and morphologically has become popular (16, 17). Mainly two methods can be used either positive in which isotopes are concentrated in the necrotic myocardium, or negative when isotopes are concentrated in the normal myocardium but not in the infarction. Examples

of the latter type of isotopes are potassium and its analogues rubidium, cesium, and thallium. Of isotopes concentrating in the infarcted myocardium, the prototypes are tetracyclines and principally technetium-labelled stannum-pyrophosphate. Both types of isotope-diagnostic methods are used to show myocardial infarction clinically. Morphological studies have shown that these methods are reliable for both quantitative and topographic assessments.

What methods are then of practical use for diagnoses of early myocardial infarction? Ordinary light microscopy cannot positively diagnose an infarction that is younger than about 8 hours. By using tetra-olium technique, this period can be shortened by about 2 hours. A very reliable but more elaborate method is to study the potassium-sodium ratio in the myocardium, the time then being reduced to 1—2 hours. During the first three hours, different enzyme histochemical methods can be employed but autolysis might affect them. Fluorescent methods are of use within the first hours, but for the diagnosis of recent infarction, tetracycline derivatives should probably be used. If isotopes are given as soon as possible, study of their distribution within the myocardium will be of great value. These methods cannot be applied to all instances of sudden heart death which occur outside the hospital. They are also difficult to apply to deaths within the hospital unless special arrangements are made to perform a post mortem soon after death. In such cases, there does not seem to be any better method than chemical determination during the first three hours after a suspected myocardial infarction. During the next three hours, fluorescence and some enzyme histochemical methods can also be used.

#### Morphological diagnosis of early myocardial infarction

##### Coronary arteries

##### Macroscopical methods

###### Without aid

###### With aid

routine (hematoxylin-eosin) stained slides, the criteria laid down by Mallory and co-workers (4) and Lodge-Patch (5) are still used. The earliest change is oedema, which is noticeable after about 2 hours. Four hours after the infarction, the cell nuclei begins to become pyknotic and after about 6 hours, changes of the cytoplasm begin to appear i.e. increased eosinophilia, shrinking, and loss of cross striation. Infiltration of polymorph-nuclear leukocytes begins about now and this change seems to be one of the best signs of an infarction as the other changes are identical with those appearing during autolysis. The leukocyte infiltration reaches its maximum after about 24 hours and persists for another one or two days and then slowly disappears. At the end of the first week, pigment filled macrophages appear together with lymphocytes and plasma-cells and fibro-blast proliferation. Later eosinophilic leukocytes might appear and collagen material is laid down. Proliferation of thin walled blood vessels begins at the end of the first week and reaches its maximum after about 4 weeks. All these changes are most pronounced in the edges of the infarction. In dating the age of an infarct, it is important to take the size of the necrosis into account.

A further histological method was published in 1972 by Bouchardy and Mamo (6). According to them, it is always possible to find especially at the edge of an infarction, myocardial fibres that are stretched, thin and wavy. This change is said to appear very quickly certainly within an hour and possibly as early as two minutes after the infarction. But most pathologists seem very sceptical about this observation and other studies have not supported the method. None the less, several papers state that no such changes were found in recent myocardial infarction.

Several methods are published about light microscopic diagnosis on specially stained slides. PAS-staining was previously used, as a diastase resistant muco-protein appears in the necrotic muscle cell. This is not apparent until the infarction is visible in also routine

stained specimens, and the method is thus useless for early diagnosis. Another more promising method is the PTAH-staining, which is said to be able to delineate rather early ischaemic lesions. With a standardized and carefully worked out technique, this method, dealt with in detail by Professor Voigt, is of great help and seems to reveal recent infarctions.

Poley and coworkers (1) introduced a further special method in 1964 based on the observation by Seiyé (8) that myocardial fibres experimentally damaged by various toxins, showed eosinophilia when stained with acid fuchsin. Poley noted that this method was somewhat unreliable, but it was re-introduced by Lie (9) with the statement that this fuchsinophilia was a very good indication of myocardial ischaemia. This is certainly not our experience or that of others (10). Lie and coworkers (11) 1971 introduced the so-called HBFp (hematoxylin basic fuchsin-picric acid) staining, which was said to be much more reliable and to be able to diagnose infarctions only a few hours old. Positive staining reactions were even reported already after 30 minutes. This positive staining, the so called fuchsinorthigia, has been much criticised as most unreliable. Although papers exist in favour of this method (12), most authors deny its value (10, 13).

Fluorescence methods can also be used histologically. The previously mentioned tetracycline method (3) gives fluorescence on both fresh sections and formalin-fixed/paraffin embedded slides. Other methods that seem promising but which have been used experimentally are acridine-orange and astraposphine staining, the latter for showing accumulation of fat (14). Acridine-orange staining which can be used on both fresh and formalin fixed material, shows ischaemic damage after about 3 hours on fresh myocardium and after about 5 hours on fixed material.

Several enzyme histochemical methods for the detection of early myocardial ischaemia have been described. It is well known that, soon after ischaemia, enzyme

activity in the myocardium changes: dehydrogenases of different types diminish in activity as do alkaline phosphatases and phosphokinases. Dehydrogenases are mostly used for this type of studies. Opinions vary about what type of enzyme is most suitable to study Succinyldehydrogenases are studied with the previously mentioned nitro-BT method (2). Other authors have used malate-dehydrogenases, or butyrate-dehydrogenase. Although there is some disagreement about how autolysis affects these methods, it seems evident that some of them can be used also several days after death. The same seems valid for estimates of creatinephosphokinase activity.

Could we use electron-microscopy to show early myocardial ischaemia? It is well known that morphological changes occur within 15 minutes after ischaemia and are well developed after about 30—60 minutes. The changes are the same as those caused by autolysis, and this makes such a method practically unusable. But it is possible to use it in experimental work.

Chemical analysis has been shown to be a reliable sign of ischaemic damage (15). Within 10—15 minutes after ischaemia, the amount of sodium is increased in the infarcted area, and potassium is lost. Also concentration of other ions, for instance magnesium and calcium, is changed. Most studies have used the potassium-sodium ratio, which decreases in ischaemic myocardium compared with normal myocardium. The estimate is independent of autolysis, and the method seems to be reliable. The disadvantage is that several parts of the myocardium must be studied and that localization and quantitation of myocardial damage is difficult.

In recent years, the use of radioactive isotopes for detecting myocardial ischaemia, both clinically and morphologically, has become popular (16, 17). Mainly the methods can be used either post mortem in which isotopes are concentrated in the necrotic myocardium, or *in vivo* where isotopes are concentrated in the normal myocardium but not in the infarction. Examples

of the latter type of isotopes are potassium and its analogues rubidium, caesium, and thallium. Of isotopes concentrating in the infarcted myocardium, the prototypes are tetracyclines and principally technetium-labelled stannum-pyrophosphate. Both types of isotope-diagnostic methods are used to show myocardial infarction clinically. Morphological studies have shown that these methods are reliable for both quantitative and topographic assessments.

What methods are then of practical use for diagnosis of early myocardial infarction? Ordinary light microscopy cannot positively diagnose an infarction that is younger than about 8 hours. By using tetrazolium technique, this period can be shortened by about 2 hours. A very reliable but more elaborate method is to study the potassium-sodium ratio in the myocardium, the time then being reduced to 1—2 hours. During the first three hours, different enzyme histochemical methods can be employed but autolysis might affect them. Fluorescent methods are of use within the first hours, but for the diagnosis of recent infarction, tetracycline derivatives should probably be used. If isotopes are given as soon as possible, a study of their distribution within the myocardium will be of great value. These methods cannot be applied to all instances of sudden heart death which occur outside the hospital. They are also difficult to apply to deaths within the hospital unless special arrangements are made to perform a post mortem soon after death. In such cases, there does not seem to be any better method than chemical determination during the first three hours after a suspected myocardial infarction. During the next three hours, fluorescent and some enzyme histochemical methods can also be used.

## Morphological diagnosis of early myocardial infarction

### Coronary arteries

### Macroscopical methods

#### Without aid

#### With aid

Tetrazolium derivatives, nitro-BT  
 Fluorescence  
 Light microscopical methods  
 Routine-stained (Htx-eosin) slides  
 Traditional histologic criteria  
 Wavy myocardial fibres  
 Special-stained slides  
 PAS (periodic acid Schiff)  
 PTAH (phospho-tungstic acid hematoxylin)  
 Acid fuchsin, fuchsinophilia  
 HBFP (hematoxylin basic fuchsin picric acid) fuchsinorrhagia  
 Fluorescence  
 Tetracyclin  
 Acridin-orange  
 Astraphosphin  
 Enzyme histochemistry  
 Dehydrogenases (succinyl lactate-malate- butyrate)  
 Phosphorylases  
 Phosphokinases  
 Electron microscopical methods  
 Morphology  
 Enzyme histochemistry  
 Chemical methods  
 Sodium (+) Potassium (-)  
 Calcium (+) Magnesium (-)  
 Isotope methods  
 Positive diagnosis  
 Technetium (stannum-pyrophosphate)  
 Tetracyclin  
 Negative diagnosis  
 Potassium, Cesium, Thallium

## References

- Robbins, S. L. Cardiac pathology — a look at the last five years. Part I Human Pathol. 5:9 1974
- Nachlas, M. M. & Shnitka, T. K. Macroscopic identification of early myocardial infarcts by alterations in dehydrogenase activity Am. J. Path. 42:379 1963
- Málek, P. Kolc, J. Zístava, V., Zák, F. & Peleška, B. Fluorescence of tetracycline analogues fixed in myocardial infarction. Cardiologia 42:303 1963
- Mallory G. K., White, P. D. & Salcedo-Salgar J.: The speed of healing of myocardial infarction a study of the pathologic anatomy in seventy-two cases. Amer Heart J 18:647 1939
- Lodge-Patch, I.: The ageing of cardiac infarcts, and its influence on cardiac rupture Brit. Heart J 13:37 1951
- Bouchardy B. & Majno, G.: A new approach to the histologic diagnosis of early myocardial infarcts. Cardiology 56 327 1972
- Poley R. W., Fobes, C. D. & Hall, M. J. Fuchsinophilia in early myocardial infarction Arch. Path 77:325 1964
- Selye, H. The chemical prevention of cardiac necrosis. The Ronald Press Co New York, 1958 p 43
- Lie, J. T.: Detection of early myocardial infarction by the acid fuchsin staining technic. Am. J. Clin. Path 50:317 1968
- Zugibe, F. T. & Zugibe, F. T.: Fuchsinophilia and fuchsinorrhagia staining techniques. Arch. Path. 96:243 1973
- Lie, J. T., Holley K. E., Kampa, W. R. & Titus, J. L. New histochemical method for morphologic diagnosis of early stages of myocardial ischaemia. Mayo Clinic. Proc. 46 319 1971
- Nayar A. & Olsen, G. J.: The use of the basic fuchsin stain in the recognition of early myocardial ischaemia. Cardio-vasc. Res. 8:391 1974
- Jakobson, S. & Raj, J. Experiences with haematoxylin basic fuchsin picric acid staining method for morphologic diagnosis of myocardial ischaemia. — An experimental study in forensic medicine. Forensic Science 8:37 1976
- Hecht, A., Korb G. & David, H. Comparative histochemical, fluorescent microscopic and electron microscopic investigations into the early diagnosis of myocardial infarcts in the rat. Virch. Arch. path Anat. 334:1 1961

- 15 Zagibe, F. T. Bell, P. Conley T. & Scandish, M. L. Determination of myocardial alterations at autopsy in the absence of gross and microscopic changes. Arch. Path. 81:409 1966.
- 16 Zaret, B. L., DeCola, V. Donabedian, R. K., Puri, S., Wolfson, S., Freedman, G. S. & Cohen, L. S. Dual radioactive study of myocardial infarction. Relationships between myocardial uptake of Potassium-43 Technetium-99m Scannous Pyrophosphate, regional myocardial blood flow and creatine phosphokinase depletion. Circ. 53:422, 1976.
- 17 Holman, B. L., Ehric, M., Lesch, M.: Correlation of acute myocardial scintigraphy with postmortem studies. Amer J Cardiol. 37:311 1976.

# Creatine kinase MB isoenzyme in diagnosis of acute myocardial infarction

Peer Grande, Claus Christiansen and Asger Pedersen

Dept. of Clinical Chemistry and Coronary Care Unit,  
Copenhagen County Hospital, GLOSTRUP DENMARK

## Abstract

In a consecutive series of 401 patients admitted to the Coronary Care Unit of the Copenhagen County Hospital at Glostrup suspected of acute myocardial infarction (AMI) less than 24 hours old, blood samples for enzyme analysis were drawn at admission and 12, 24, 36, 48 and 72 hours later and ECG in 9 leads was recorded daily during the first week. From usual diagnostic criteria — clinical symptoms, ECG-findings, and enzyme analyses, not including and not knowing the results of CK—MB analyses — the series was divided into patients with AMI and those without AMI.

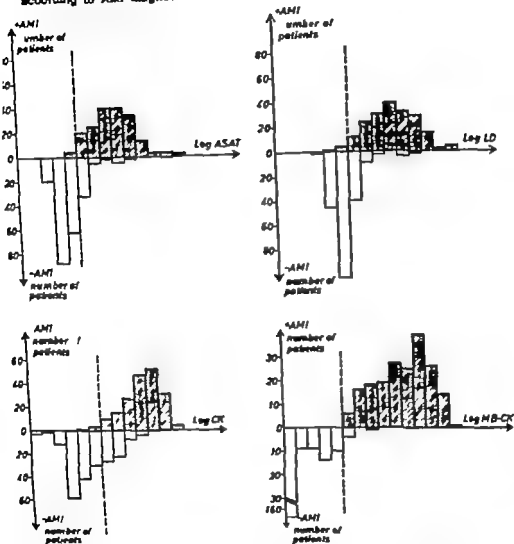
Comparison is made between the predictive values in the diagnosis of AMI of a positive and a negative result (PV pos. and PV-neg.) of either of the tests ECG and serum levels of aspartate aminotransferase (ASAT) lactate dehydrogenase (LD) creatine kinase (CK) and MB-fraction of CK determined by electrophoresis. The salient features were PV-neg. i.e. diagnostic sensitivity was low (0.78) for ECG but high for all enzyme tests (0.97–1.00) PV-pos. i.e. diagnostic specificity was rather low for the three standard enzymes (0.73–0.87) but high for CK—MB (0.98) and also for ECG (1.00). Thus, determination of CK—MB seems to offer the best combination of a high sensitivity as well as specificity in the diagnosis of AMI. However, the time factor should be kept in mind as positive results

of CK—MB can only be expected during the first 30–50 hours after the onset of the AMI.

The early and reliable identification of acute myocardial infarction (AMI) is a common and important clinical challenge. The detection of rising blood levels of certain enzymes known to be released from an infarcted myocardium has become an essential part of this clinical diagnosis. However, the enzyme tests now in general use in the diagnosis of AMI — the aspartate aminotransferase (ASAT), the lactate dehydrogenase (LD), and the creatine kinase (CK) — apparently show only a limited specificity for the purpose and the number of false positive results in these patients are probably rather consistent (1–10).

The separation of the CK into the three isoenzymes, MM, MB, and BB, seems to offer possibilities for significantly increasing the specificity of the test (4, 6, 8). Analyses of tissue extracts indicate that the isoenzyme CK—MB is found only in the myocardium in amounts sufficient to cause significant increase in serum concentration (2, 4, 6, 14). The clinical experience from a large group of patients, reported below, seems to confirm the presumption that determination of CK—MB levels is the hitherto most specific and sensitive diagnostic test for a fresh AMI.

**Fig 1**  
Frequency distribution of ASAT, LD, CK, and MB-CK in 401 patients grouped according to AMI diagnosis.



## Patients and methods

### Patients

Criteria for entering the study were: (1) Clinical suspicion of AMI begun less than 24 hours before admission, and (2) availability of three assays with 12 hours interval of each of the enzyme tests within their respective diagnostic period LD 12–96

hours, ASAT and CK 6–60 hours, and CK-MB 6–48 hours after the onset of symptoms.

During a period of 6 months (October 1976–March 1977) 466 patients were admitted to the Coronary Care Unit of the Copenhagen County Hospital in Glostrup with the suspicion of an AMI less than 24 hours old.



**Predictive values of negative and positive outcomes of enzyme analyses and of ECG in 401 patients of whom 192 had AMI.**

Results	Predictive value				
	CK—MB	CK	ASAT	LD	ECG
Negative	1 00	0 98	0 97	0 98	0 78
Positive	0 93	0 73	0 87	0 77	1 00

In 45 of those patients, data collection did not fulfill the criteria, as 8 patients died and 37 were discharged before sufficient data were obtained. In another 20, the diagnosis AMI could not be definitely established.

The remaining 401 patients were classified into one of two groups. One of 192 patients (146 men and 46 women, age 36—88 years, mean 62.2 years) fulfilled the criteria for the diagnosis AMI. The second group of 209 patients (140 men and 69 women, age 36—90 mean 59.8 years) did not meet the same criteria.

### Methods

The diagnosis AMI was made in accordance with the criteria suggested by WHO (16) thus comprising clinical symptoms, ECG findings, and results of ASAT, LD, and CK, but not regarding the results of the CK—MB analysis.

ECG in 3 bipolar extremity and 6 unipolar precordial leads was recorded daily during the first 5 days and at least once a week for the subsequent period.

Blood samples were drawn immediately after admission and subsequently about 12, 24, 36, 48, and 72 hours later. All enzyme analyses were made from unhemolysed serum, according to the recommended methods (11, 12). Rate measurements for the kinetic methods were made at 37 °C with an LKB 8600 reaction rate analyser and an Hitachi Perkin-Elmer recorder.

CK—MB determinations were performed by electrophoresis on agarose gel and quantification by fluorescence scanning (3).

### Calculation of the results

The result of each test parameter was considered separately and without knowledge of the other. The enzymatic parameters were considered pathological if at least one of the respective assays showed activity above the upper discriminative limit. ECG was evaluated in accordance with the WHO recommendations (16).

To make a clear comparison of the test parameters, the predictability was calculated as follows: The predictability of positive test (PV pos) = the number of patients diagnosed as AMI showing pathological parameters divided by the total number of patients with a pathological test result. The predictability of a negative test (PV neg) = the number of patients without AMI showing non-pathological test parameters divided by the total number of subjects with a negative test result. The efficacy of a test is defined as the sum of true positive and true negative results divided by the total number of tests performed.

### Results

The figure gives the frequency distribution of ASAT, LD, CK, and CK—MB. The discriminative limit is indicated by the dotted line. The limit is placed with the object of avoiding false negative results rather than false positive ones.

The above table lists the predictive value of each test parameter. The predictive value of negative test demonstrate almost identical results for all four enzymatic assays. ECG however shows a significantly lower

PV-neg., i.e. a low diagnostic sensitivity in 61 out of the 192 patients diagnosed as AMI, the ECG showed no characteristic infarct pattern, usually due to the presence of bundle branch block or sequelae of previous AMI. The values of PV-post demonstrate that, in diagnostic specificity, characteristic electrocardiogram and a pathological CK-MB are superior to the standard enzyme results. The efficacy based on the indicated discriminative limits is as follows: ASAT 0.90 LD 0.85 CK 0.83 CK-MB 0.99 and ECG 0.85.

## Discussion

The value of any new test must rest on comparisons with the known advantages and disadvantages of existing test, and its application to common use should depend on convincing evidence of its superiority.

In the diagnostic procedure of AMI, there is little doubt that serum enzymes have been clinically useful and important. In clinical routine, emphasis has usually been placed on serial enzyme studies because of the generally low specificity of most enzymes applied in this connection. Thus, CK can be elevated by intramuscular injections, lung disease, cerebrovascular disease, convulsions, chronic alcoholism (5), and strenuous exercise (13).

In the evaluation of a diagnostic test such as CK-MB, a major problem is the lack of control diagnostic procedure. Autopsy data will be available only in a minority and generally the tested parameter will be part of the diagnostic criteria against which it is tested. In our series, CK-MB analysis was kept out of the diagnostic criteria, thus probably slightly improving the specificity of the other three enzymes compared with that of the CK-MB.

Apart from its value in the qualitative diagnosis of AMI, serial enzyme determination might also give a good picture of the infarct size and provide useful prognostic index (9) and also measure of the effect of any attempt to restrict the extension of infarction (7).

The frequency distribution, as presented in Fig. 1 shows a varying degree of overlapping between the activity areas in whom patients with and those without AMI will be found. The frequency of false positive and false negative results is determined by the position of the discriminative limit, i.e. the vertical dotted line placed according to clinical considerations. The best possible test parameter will be the one that shows a frequency distribution whose area of overlapping is smallest. None of the four distributions is perfect, but CK-MB is obviously considerably better than the others.

The predictability is estimated from the point of view that in the practical use of a diagnostic test, the likelihood of a disease being present when a test result is pathological, or absent when a test result is normal, is generally preferable to the reverse state of affairs: the likelihood that, in a sick person the test is pathological, and in a normal person the test shows a normal result (15-17).

From the table, it is evident that CK-MB has the highest diagnostic sensitivity (PV-neg.) and a diagnostic specificity (PV-pos.) almost as high as that of the ECG. This suggests that a pathological test result of the CK-MB or the ECG is almost diagnostic of AMI. On the other hand, failure to demonstrate pathological serum enzyme levels within the diagnostic period in the case of ASAT LD and CK is strongly suggestive, and in the case of CK-MB presumably safe evidence, that AMI is not present. However due regard must be paid to the time factor. After more than 30-50 hours after the supposed time of onset of AMI the course of standard enzymes is usually more relevant to the diagnosis than are the values of CK-MB.

## Acknowledgements

The authors acknowledge the technical assistance of Mrs. Hanne Kohn, Mrs. Rigmor Jensen, and Mrs. Lene Smith.

## References

- 1 Goldberg, D M., Winfield D A. Diagnostic accuracy of serum enzyme assays for myocardial infarction in a general hospital population. *Br Heart J* 34 597 1972.
- 2 Grande, P., Prætorius, E., Christiansen C. Kreatin kinase isoenzymbestemmelse i diagnosticeringen af akut myokardieinfarkt. *Ugeskr Læg* 140 1546 1978
- 3 Grande, P., Christiansen, C., Næstoft, J. Creatine kinase isoenzyme assay by electrophoresis. Submitted to *Scand. J Clin. Lab. Invest.*
- 4 Klein, M S. Shell W E., Sobel B E. Serum creatine phosphokinase (CPK) isoenzymes after intramuscular injections, surgery and myocardial infarction. *Cardiovasc. Res.* 7 412, 1973
- 5 Nevins, M A. Saran, M., Bright, M., Lyon, L. J. Pitfalls in interpreting serum creatine phosphokinase activity. *JAMA* 224 1382 1973
- 6 Roberts, R., Godwa K. S. Ludbrock P A., Sobel B E. Specificity of elevated serum MB creatine phosphokinase activity in the diagnosis of acute myocardial infarction. *Am. J Cardiol* 36 433 1975
- 7 Shell W E., Sobel B E. Protection of jeopardized ischaemic myocardium by reduction of ventricular afterload. *N Engl J Med.* 291 481 1974
- 8 Smith, A F., Radford D., Wing, G P. Oliver M F. Creatine kinase MB isoenzyme studies in diagnosis of myocardial infarction. *Br Heart J* 38 225 1976
- 9 Sobel, B E., Breshnahn, G F. Shell W E. Yoder R. D. Estimation of infarct size in man and its relation to prognosis. *Circulation* 46 640 1972.
- 10 Sobel, B E., Shell W E. Serum enzyme determinations in the diagnosis and assessment of myocardial infarction. *Circulation* 45 471 1972
- 11 Recommended methods for the determination of creatine kinase in blood. *Scand. J Clin Lab Invest.* 36 711 1976
- 12 Recommended methods for the determination of four enzymes in blood. *Scand J Clin. Lab. Invest.* 33 291 1974
- 13 Swaiman, K., Awas, E. A. Creatine phosphokinase and other serum enzyme activity after controlled exercise. *Neurology (Minneapolis)* 14 977 1964
- 14 Van Der Veen K. J. Willebrands, A F. Isoenzymes of creatine phosphokinase in tissue extracts and in normal and pathological sera. *Clin Chim Acta* 13 312, 1966
- 15 Vecchio, T J. Predictive value of a single diagnostic test in unselected populations. *N Engl J Med.* 274 1171 1966
- 16 WHO Report of the fourth working group regional office for Europe, Copenhagen 1970.
- 17 Wulff H R. In rationel klinik, p 100 ff. Munksgaard, Copenhagen 1973

# Serial CPK determinations after acute myocardial infarction The possible use of this technique in objective evaluation of myocardial infarction treatment.

E Lorentsen, D Scott and H Steensland

Diakonissehusets hospital Dept of Medicine OSLO NORWAY

Serial serum CPK determination during the first hour after the initial elevation of enzyme activity following acute myocardial infarction can be used to anticipate the further development in serum CPK activity and to predict the infarct size in experimental dog studies and in patients with acute myocardial infarction (2, 3). However in patients, the prediction in single individual is only valid if the infarction is sudden and definite, similar to the experimental model, which applies to approximately 30 per cent of the patients. (1) In patients with re-infarction or with gradual progression of the necrotic area, the prediction fails (1).

The method of serial CPK determinations has also been used to study the effect of treatment that might protect jeopardized noninfarcted myocardial cell from necrosis (2, 3, 4). So far the results of reperfusion by release of constricting coronary artery cuff in dogs, the administration of propranolol in dogs, and the administration of trimetaphane in hypertensive humans has been reported.

In these reports, the curve of serial CPK determinations given shows rapid and dramatic fall in CPK activity following the treatment. If this fall reflects salutary effect of the treatment, it provides simple method for appraising the ability of different kinds of treatment in limiting the extent of myocardial cell necrosis. Complicated mathematical calculations would be unnecessary - observation of drop in CPK activity would

indicate beneficial effect. The present work studied whether such a visible drop in the serum CPK level could be obtained after "myocardial protection treatment".

## Material and methods

Five patients with acute myocardial infarction were given 5 mg of propranolol intravenously for 5 minutes, and 3 patients were treated with intravenous infusion of phenolamine for 3-4 hours. The serum CPK activity was determined in blood samples obtained at 1/2-2-hourly intervals. The treatment was initiated 5-17 hours after the onset of chest pain.

## Results

Fig. 1 and 2 show the results. The treatment did not produce drop in the serum CPK activity in any patient. This observation agrees with the clinical impression. The patients did not benefit from the treatment. We therefore refrained from further experiments.

## Comments

The rather disappointing results led us to scrutinize the above-mentioned presented curves (2, 3, 4). It is rather bewildering that the drop in CPK activity shown is far greater than the decay rate. Even if all the cells, both the jeopardized ones and the irreversibly damaged, immediately ceased to release CPK, the slope of the curve would

## References

- 1 Goldberg, D M., Winfield, D A. Diagnostic accuracy of serum enzyme assays for myocardial infarction in a general hospital population *Br Heart J* 34 597 1972
- 2 Grande, P., Prætorius, E., Christiansen, C. Kreatin kinase isoenzymbestemmelse i diagnoseringen af akut myokardieinfarkt. *Ugeskr Læg* 140 1546, 1978
- 3 Grande P., Christiansen C., Næstoft, J. Creatine kinase isoenzyme assay by electrophoresis. Submitted to *Scand. J Clin. Lab. Invest.*
- 4 Klein, M. S. Shell W E., Sobel B E. Serum creatine phosphokinase (CPK) isoenzymes after intramuscular injections, surgery and myocardial infarction. *Cardiovasc. Res* 7 412, 1973
- 5 Nevins, M. A. Saran, M., Bright, M., Lyon, L. J. Pitfalls in interpreting serum creatine phosphokinase activity *JAMA* 224 1382, 1973
- 6 Roberts, R., Godwin, K. S. Ludbrook, P A., Sobel B E. Specificity of elevated serum MB creatine phosphokinase activity in the diagnosis of acute myocardial infarction. *Am J Cardiol* 36 433 1975
- 7 Shell W E., Sobel B E. Protection of jeopardized ischaemic myocardium by reduction of ventricular afterload *N Engl J Med* 291 481 1974
- 8 Smith A F. Radford, D. Wing G P., Oliver M F. Creatine kinase MB isoenzyme studies in diagnosis of myocardial infarction *Br Heart J* 38 225 1976
- 9 Sobel B E., Breshnahn G F., Shell W E. Yoder R. D. Estimation of infarct size in man and its relation to prognosis. *Circulation* 46 640, 1972
- 10 Sobel B E., Shell W E. Serum enzyme determinations in the diagnosis and assessment of myocardial infarction. *Circulation* 45 471 1972.
- 11 Recommended methods for the determination of creatine kinase in blood. *Scand. J Clin. Lab. Invest.* 36 711 1976
- 12 Recommended methods for the determination of four enzymes in blood *Scand J Clin. Lab. Invest* 33 291 1974
- 13 Swauman, K., Awas, E. A. Creatine phosphokinase and other serum enzyme activity after controlled exercise. *Neurology (Minneapolis)* 14 977 1964
- 14 Van Der Veen, K. J. Willebrands, A F. Isoenzymes of creatine phosphokinase in tissue extracts and in normal and pathological sera *Clin. Chim. Acta* 13 312, 1966
- 15 Vecchio T J. Predictive value of a single diagnostic test in unselected populations. *N Engl J Med.* 274 1171 1966.
- 16 WHO Report of the fourth working group regional office for Europe, Copenhagen 1970
- 17 Wulff H R. In *rationel klinik*, p 100 ff Munksgaard, Copenhagen 1973

# The predictive value of myocardial scintigraphy with $^{99m}$ technetium pyrophosphate in diagnosing acute myocardial infarction

P F Høllund-Carlson J Badskjær, J Boetius Hertz, O Helmer Sørensen I Christiansen and A. Uhrenholdt

Dept of Clinical Physiology and Medical Department, Cardiological section, Hvidovre hospital COPENHAGEN DENMARK

## Abstract

Myocardial scintigraphy with  $^{99m}$ technetium-pyrophosphate was performed in two selected groups of patients, consisting of 20 who had acute myocardial infarction (AMI) clinically and 18 who had no AMI clinically. The purpose was to estimate the value of this method in the detection or disproof of AMI compared with usual procedures (ECG and serum enzyme determination — GO-transaminase and  $\alpha_1$ -fraction of LDH).

Each of the 20 patients with clinical AMI had positive scintigrams. There were no false negative findings. Out of 18 without AMI, 15 had negative scintigrams; in the other 3 scintigraphic findings were false-positive.

The prevalence of AMI among patients admitted to the cardiological department was 0.39. In this population of patients, the calculated predictive value of a positive scintigram was 0.80 whereas the predictive value of a negative was 1.0. In patients admitted to the coronary care unit, the prevalence of AMI was 0.51; the corresponding predictive values of a positive scintigram was 0.86 and of a negative 1.0.

The identity between scintigraphic and electrocardiographic infarct localization was good. Infarct size estimated by scintigraphy was not significantly correlated to the maximum elevation of serum enzyme concentration.

In patients suspected of having AMI, it is

highly probable that a negative scintigram obtained from day 2 to day 6 after the onset of symptoms will rule out the presence of acute myocardial infarction.

## Introduction

The diagnosis of acute myocardial infarction (AMI) based on the occurrence of chest pain, sequential electrocardiographic changes, and elevation of serum enzyme activity cannot always be made with certainty. In recent years, the search for a safer method for detecting or excluding the presence of AMI has led to the use of isotope scintigraphic technique for visualizing the infarcted area of the myocardium (2, 3, 9).

The purpose of this study was to determine the predictive value of a positive and a negative myocardial scintigram.

## Material and methods

20 patients with and 20 patients without clinical AMI were investigated. The diagnosis was based on the simultaneous presence of two of the following three phenomena: typical history of disease, characteristic ECG-changes, and temporary elevation of serum enzyme activity (serum aspartateaminotransferase [ASAT] and  $\alpha_1$  fraction of serum-lactate dehydrogenase [LDH]). Fourteen patients in the group with AMI had transmural infarction, 2 had non-penetrating (non-transmural) infarction, 3 had subendocardial infarction, and one had left bundle branch

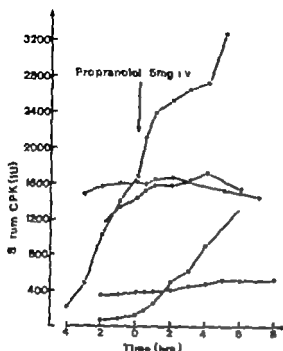


Fig 1 Serial CPK determinations in 5 patients with acute myocardial infarction treated with 5 mg of propranolol i.v.

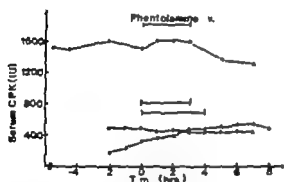


Fig 2 Serial CPK determinations in 3 patients with acute myocardial infarction treated with phentolamine (0.15–0.2 mg/min).

not be as steep as presented. This puzzling problem makes us doubt the use of serial CPK determinations as an indication of myocardial cell protection. The rapid fall in CPK activity seems to represent an artefact caused by the intervention.

It might be argued against our results that the treatment was given rather late in the course of the infarction when most of the irreversible damage is probably already done

A lack of effect during this stage is not surprising. However the same argument can be presented against previously reported studies in patients in whom the treatment was started about 13 hours after the onset of chest pains. None the less, a reduction of infarct size from 53 CPK grammes equivalent to 27 was obtained after trimetaphane treatment in a hypertensive patient. It is difficult to understand that the effect of treatment can be so extensive at this stage.

Recently the reservation was made that the evaluation of treatment can only be performed in groups of patients and not in the individual (5). However until the drastic fall in serum CPK activity is explained the applicability of the method must be questioned even when used in groups of patients.

This presentation was not primarily intended to submit our own observations, but to find an opportunity to pinpoint previously published results that could be misleading.

## References

- 1 Bleifeld, W. H., Hanrath, P. and Mathey, D. Serial CPK determinations for evaluation of size and development of acute myocardial infarction. *Circulation* 53 suppl. I: 108, 1976.
- 2 Shell, W. E., Lavelle, J. F., Covell, J. W. and Sobel, B. E. Early estimation of myocardial damage in conscious dogs and patients with evolving acute myocardial infarction. *J. Clin. Invest.* 52: 2579, 1973.
- 3 Shell, W. E. and Sobel, B. E. Protection of jeopardized ischaemic myocardium by reduction of ventricular afterload. *N. Engl. J. Med.* 291: 841, 1974.
- 4 Shell, W. E. and Sobel, B. E. Biochemical markers of ischaemic injury. *Circulation* 53 suppl. 1: 98, 1976.
- 5 Sobel, B. E. Biochemical and morphological changes in infarcting myocardium. In E. Braunwald, ed. *The Myocardium: Failure & Infarction*. HP Publishing Co. Inc. New York, 1975.



Fig 2. Positive (4+) scintigrams of patient shown in A) anterior B) 45° left anterior oblique with extensive acute anterior wall infarction C) left lateral views.



Fig 3. Positive scintigrams of patient with acute infero-lateral infarction shown in A) anterior B) 45° left anterior oblique C) left lateral views.

the 18 without clinical AMI had negative scintigram scintigraphic findings were positive the remaining three. Nosographically this means that the probability of a positive scintigram in patients with AMI was  $\frac{20}{20} = 1.0$ , whereas the probability of a negative scintigram in those without AMI was  $\frac{13}{18} = 0.83$ .

The diagnostic probabilities were calculated with Bayes theorem (14). The prevalence of AMI among patients admitted to the cardiological department in Hvidovre hospital was 0.51. The corresponding predictive value of positive scintigram was 0.80, and that of negative scintigram was 1.0.

Table I. Scintigraphic compared with clinical diagnosis.

	SCINTIGRAPHY	
	+	-
AMI	20	0
-	3	15

In patients admitted to the coronary care unit in Hvidovre hospital, the prevalence of AMI was 0.51. The corresponding figure for the predictive value of a positive scintigram was 0.86 and for a negative, 1.0.



block, which made judgement of the ECG impossible.

Two were excluded from the control group of patients without clinical AMI. One because she had streptococcus endocarditis. The other because he had earlier had myocardial infarction.

Informed consent was obtained from each patient on entering the study.

The investigation was made with a gamma camera with high resolution collimator collection 500 000 counts one hour after the intravenous injection of 15 mCi  $^{99m}\text{Tc}$  pyrophosphate ( $\text{Tc PYP}$ ). Pictures were obtained in the anterior (AP), the left anterior oblique (LAO) and the left lateral (LL) projections.

The scintigrams were evaluated jointly by two investigators without previous knowledge of the clinical diagnosis. The degree of intensity of myocardial uptake was graded according to an arbitrary scale described by Parkery et al (8): 0 (no activity), 1+ (questionable activity), 2+ (definite activity), 3+ and 4+ (increasing degrees of activity within the infarct zone). Zero and 1+ were considered negative; 2+, 3+ and 4+ in only one projection were considered positive. Infarct localizations were estimated as antero-septal, antero-apical, antero-lateral and inferior or combinations of these.

Infarct size was estimated as follows: small (smaller than the width of 2 ribs with interjacent intercostal space), medium (corresponding to the width of 2 ribs), large (larger than the width of 2 ribs).

Electrocardiographic infarct localization was defined as follows: antero-septal ( $V_1-3$ ), antero-apical ( $V_4-6$ ), antero-lateral ( $V_4-6$ , AVL, I), inferior (II, III and AVF).

## Results

Figure 1A-C shows a normal (negative) scintigram of a patient without clinical evidence of AMI.

Figure 2A-C demonstrates typical scintigrams in three projections from a patient with AMI. Note typical doughnut or horse shoe appearance of increased myocardial uptake surrounding central area with sparse activity.

Figure 3A-C demonstrates an inferior infarction characterized by a disc-like activity in the diaphragmatic wall. Being viewed from the side in all three projections, the infarct size cannot be estimated and a central decrease in activity cannot be observed. In the patients with AMI, scintigraphy was performed within day 1 to day 6 of observation (mean 3.0 days). Each of the 20 patients had a positive scintigram (Table I). Fifteen of



Fig 1 Negative (normal) myocardial scintigrams of a patient without acute myocardial infarction shown in the three standard views: A) anterior, B) 45° left anterior oblique, C) left lateral.

Note activity in the sternum in the middle of A) and to the left in B) and activity in the vertebral column behind ribs in the middle of B) and in the right in C).

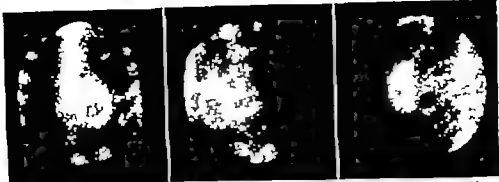


Fig. 2. Positive (4+) scintigrams of patient shown in A) anterior B) 45° left anterior oblique C) left lateral views with extensive acute anterior wall infarction.



Fig. 3. Positive scintigrams of patient with acute infero-lateral infarction shown in A) anterior B) 45° left anterior oblique C) left lateral views.

the 18 without clinical AMI had negative scintigrams scintigraphic findings were positive the remaining three. Nosographically this means that the probability of positive scintigram in patients with AMI is  $\frac{20}{20} = 1.0$ , whereas the probability of negative scintigram in those without AMI was  $\frac{15}{18} = 0.83$ .

The diagnostic probabilities were calculated with Bayes' theorem (14). The prevalence of AMI among patients admitted to the cardiological department in Hvidovre hospital was 0.51. The corresponding predictive value of positive scintigram was 0.80, and that of negative scintigram was 1.0.

Table 1. Scintigraphic compared with clinical diagnosis.

	SCINTIGRAPHY	
	+	-
AMI	20	0
-	3	15

In patients admitted to the coronary care unit in Hvidovre hospital, the prevalence of AMI was 0.51. The corresponding figure for the predictive value of positive scintigram was 0.86 and for negative 1.0.

Table II Scintigraphic compared with electrocardiographic infarct localization

	SCINTIGRAPHY	
	Anterior	Inferior
Anterior ECG	13 )	—
Inferior	—	7

\*) 1 patient had left bundle branch block

Scintigraphic infarct size was not significantly correlated to the maximum elevation of serum enzyme activity in patients with AMI

In the group of patients with clinical AMI 7 had inferior infarction on both scintigram and electrocardiogram 13 showed an anterior infarction on the scintigram and 12 of them had corresponding electrocardiographic localization. The other patient had left bundle branch block that did not permit determination of infarct localization, but autopsy one week later revealed recent infarction in the anterior wall of the left ventricle.

Table III gives a comparison of scintigraphic and electrocardiographic subdivisions of anterior wall infarctions.

Table III Anterior infarct localization Thirty four scintigraphic localizations compared with 32 electrocardiographic localizations.

		SCINTYGRAPHY			
ECG		Antero-septal	Antero-apical	Antero-lateral	Undetected
	Antero-septal	8			2
	Antero-apical		12		
	Antero-lateral	1		7	2
	Undetected		2	4	

Our material did not contain either electrocardiographic or scintigraphic posterior infarctions.

## Discussion

Since 1974  $^{99m}\text{Tc}$  labelled radiopharmaceuticals which sequester in acutely infarcted myocardium have been used clinically for positive scintigraphic visualization of AMI. Among several compounds, the bone-seeking technetium phosphates have gained the greatest popularity. In animals, they concentrate in infarcted myocardial tissue with an infarct/normal myocardium ratio of about 10 (2). It was recently shown (4) that Tc PYP is superior to both  $^{99m}\text{Tc}$  tetracycline and  $^{99m}\text{Tc}$ -glucoheptonate in detecting acute myocardial infarction.

The mechanism of uptake in infarcted, and possibly severely ischaemic, myocardial tissue is not known with certainty. A certain perfusion is necessary for the tracers to reach their target (7-9) and they are likely to localize primarily in the border zone of the infarcted area. Necrotic myocardial cells accumulate calcium ions. These are probably bound in hydroxyapatite like structures that have been observed in infarcted and perhaps also in ischaemic myocardial cells (3, 8, 9, 10).

We found a positive scintigram in each

of the 20 patients with clinical AMI. This corresponds to the findings of other investigators, who have no false negative scintigrams with Tc-PYP where myocardial scintigraphy was carried out from 18 hours to 6 days after the onset of symptoms. The false-positive scintigrams that we found might be due to insufficient selection of the control group. On the other hand, some patients with heart aneurysm (1, 6) and unstable angina (13) have been reported to demonstrate positive scintigrams in the absence of clinical evidence of AMI. False-positive scintigrams have also been described in patients after left radical mastectomy in a patient with carcinoma in the left lung treated with X rays (11) and in an instance of secondary hyperparathyroidism with complicating uraemic pericarditis (3).

In patients with AMI positive scintigrams with T-PYP and other bone-seeking technetium labelled phosphates will become negative within one or two weeks after the onset of symptoms, unless left ventricular aneurysm or aneurys develops. The use of Tc PYP after this period makes the demonstration of repeated infarcts possible. With  $^{99m}\text{Tc}$  tetracycline and  $^{201}\text{Tl}$  thallium, scintigrams will be positive in patients with old infarctions.

In our investigation, it was possible to distinguish between anterior and inferior infarctions (Table II). It was also possible to estimate the localization and extension of anterior infarctions with satisfactory accuracy (Table III). Two antero-apical localizations were overlooked on the scintigrams undoubtedly accumulation of activity in the sternum made interpretation difficult. In two patients, scintigrams did not reveal an antero-lateral localization which was registered electrocardiographically. One of these patients had a subendocardial infarction with

rather faint and diffuse accumulation of activity whereas the other had an inferior infarction both electrocardiographically and scintigraphically but ECG also showed changes in lead V<sub>6</sub>. Conversely 4 antero-lateral and 2 antero-apical infarct localizations that were not seen on the ECG were

described on the scintigrams. In these cases, scintigraphy overestimated the extent of infarction, indicating that Tc-PYP might not only mark necrotic myocardial tissue, but possibly also severely ischaemic myocardial cells, as has been shown experimentally in animals (7).

In one patient with electrocardiographical inferior and antero-lateral infarct, the scintigraphic localization was inferior and antero-septal. Here too, the explanation might be labelling of ischaemic cells, because shortly afterwards the patient developed antero-septal infarction that was later verified at autopsy.

The method is not specific, but applied to patients admitted to coronary care unit with suspicion of AMI, the predictive value of a positive scintigram was reasonably high (0.86). Naturally this information has limited value, because the scintigraphic method was compared with other investigations (ECG and serum enzyme activity) whose diagnostic value is not definitely known. However in patients with AMI, the scintigrams almost always seem to be positive on the second or third day after the onset of symptoms. Combined with a predictive value of a negative scintigram of 1.0, this implies that a negative scintigram obtained on the third day of observation can exclude with considerable certainty the presence of AMI (defined according to current criteria).

In conclusion, we find that the method has its most important diagnostic values where the electrocardiogram might fail to disclose an acute myocardial infarction in patients with bundle branch block, old myocardial infarction, or subendocardial infarction (12). Our investigation showed that a negative myocardial scintigram will rule out the presence of AMI with a high degree of probability. Time will show whether the method will gain additional importance in the early detection of postinfarction aneurysms, in estimating the infarct size, particularly during infarct-limiting treatment, and hopefully become useful tool for a better understanding of the pathophysiology of acute myocardial infarction.

## References

- 1 Ahmad, M., Dubiel J P., Verden, T A., Jr & Martin R H Technetium 99m stannous pyrophosphate myocardial imaging in patients with and without left ventricular aneurysm  
*Circulation* 53 883 1976
- 2 Bonte F J., Parkey R. W., Graham K. D & Moore J G Distributions of several agents useful in imaging myocardial infarcts.  
*J Nucl. Med* 16 132 1975
- 3 D'Agostino A N & Chiga, M Mitochondrial mineralization in human myocardium  
*Am J Clin Pathol* 53 820 1970
- 4 Holman, B L. Tanaka, T T & Lesch M Evaluation of radiopharmaceuticals for the detection of acute myocardial infarction in man  
*Radiology* 121 427 1976
- 5 Janowitz, W R. & Serafini, A N Intense myocardial uptake of  $^{99m}\text{Tc}$  diphosphonate in a uremic patient with secondary hyperparathyroidism and pericarditis: case report.  
*J Nucl Med* 17 896 1976
- 6 Kelly R J., Cowan R. J., Maynard, C D Headly R N & Kahl F R. Localization of  $^{99m}\text{Tc}$  Sn Pyrophosphate in left ventricular aneurysms.  
*J Nucl Med* 18 342 1977
- 7 Marcus, M. L., Tomanek, R. J., Ehrhardt, J C Kerber R E., Brown D D & Abboud, F M Relationship between myocardial perfusion, myocardial necrosis, and technetium 99m pyrophosphate uptake in dogs subjected to sudden coronary occlusion.  
*Circulation* 54 647 1976
- 8 Parkey R. W Bonte F J Meyer S. L., Atkins, J M., Currey G L, Stokely E. M & Willerson, J T A new method for radionuclide imaging of acute myocardial infarction in humans.  
*Circulation* 50 540 1974
- 9 Poe N D Present status of positive scintigraphic imaging of myocardial infarction.  
*Scand. J Clin Lab. Invest.* 36 401 1976
- 10 Shen A C & Jennings, R B Myocardial calcium and magnesium in acute ischemic injury  
*Am J Pathol* 67 417 1972.
- 11 Som J S., Burdine, J A & Beal, W Myocardial localization of  $^{99m}\text{Tc}$ -pyrophosphate without evidence of acute myocardial infarction.  
*J Nucl Med* 16 944 1975
- 12 Willerson J T., Parkey R. W., Bonte F J Meyer S L. & Stokely E. M Acute subendocardial myocardial infarction in patients. Its detection by technetium 99m stannous pyrophosphate myocardial scintigrams.  
*Circulation* 51 436 1975
- 13 Willerson, J T Parkey R W., Bonte F J., Meyer S L., Atkins, J M & Stokely E. M Technetium stannous pyrophosphate myocardial scintigrams in patients with chest pain of varying etiology  
*Circulation* 51 1046 1975
- 14 Wulff H. R. Rationel klinik  
Munksgaards Forlag Kobenhavn 1973

# The variability of ST segment in the early phase of acute myocardial infarction

K Thygesen, M Hørdér B Lyager Nielsen  
and P Hyltoft Petersen

Dept. of Medicine B and Dept. of Clinical Chemistry  
Odense University hospital, ODENSE, DENMARK

A grant from the Danish Heart Foundation supported this investigation.

## Abstract

The ST segment elevation was measured hourly via single surface unipolar lead for 48 hours after admission, in 30 patients with acute myocardial infarction (AMI) admitted, on average 2 hours after the onset of symptoms. In 14 patients with anterior AMI the recordings were made through the precordial lead that initially showed the maximum ST elevation. In 16 patients with inferior AMI, the aVF lead was used. Twenty-five control patients without AMI had the ST deviation measured hourly for 24 hours. 15 of them had the recording made via the V<sub>4</sub>, aVF being used with the others. Our data for the reliability of the method showed that the variations in ST deviations in the control group were of the same magnitude as those observed with the measuring error of the method itself.

The investigation showed that the spontaneous course of the hourly measured ST elevation in the early phase of AMI was marked by pronounced variability and that this applied to both anterior and inferior infarction. The intra-individual patient variation of the ST elevation was significantly greater than in the control group of patients. The inter-individual patient variation of the ST elevation with AMI was also significant. The ST elevation was correlated to heart rate, mean arterial blood pressure, heart rate multiplied by systolic blood pressure, and

respiratory rate and it could be shown partly that there was a significant dispersion of the correlation coefficients within the separate correlation groups, and partly that the correlation coefficients were variable between the groups. It was also shown that nasal oxygen therapy and cardiac pain had no bearing on ST elevation. The variability of ST elevation was thus most often unexplainable and only rarely accounted for by alterations in the clinical status.

It is generally accepted that ST segment elevation in the ECG is one of the characteristic features of acute myocardial infarction (AMI) but the electrophysiological basis of changes in the ST segment in myocardial ischaemia has not been completely clarified (1).

In recent years, several investigations have been carried out where ST elevation has been used as a quantitative indicator of myocardial ischaemia. With multiple leads and epicardial and precordial mapping techniques, the sum of ST elevations has been used as an estimate of the extent of ischaemic injury after coronary occlusion in animal and after AMI in man (2-8, 9, 12, 13). However, from the theoretical and experimental bases of ST segment deviation, it has been suggested that ST segment mapping is not a reliable measure of myocardial ischaemia (4, 5). Other investigators have pointed out the limitations

of this method when used for the bedside estimate of ischaemic injury (11-15)

These studies suggest that there is a considerable variability of the ST elevation after AMI. Therefore, in an attempt to elucidate this problem we have studied the ST elevation from hour to hour in a single surface lead for the first 2 days after admission of patients with AMI and have related the ST elevation to ST deviations measured hourly in patients without AMI. In addition, the ST elevations in patients with AMI have been related to heart rate, blood pressure, respiratory rate, retrosternal pain and oxygen treatment—clinical factors that can be associated with or can influence, myocardial ischaemia.

## Material and method

### 1 The patient group

The investigation includes 30 patients with AMI admitted to the coronary care unit (CCU) of the Odense University hospital, on average 2 hours after the onset of symptoms. Their average age was 63 years. There were 22 men and 8 women. Patients with pericarditis, disturbances of electrolyte balance, a QRS duration  $\geq 0.12$  seconds, or patients under drug therapy possibly affecting the ST segment (digitalis, isoproterenol, beta adrenergic blocking drugs) were not admitted to the study.

The patients were treated according to the usual procedure of the CCU: i.e. rest in bed, morphine, anti arrhythmic drugs, and diuretics as required and oxygen via a nasal catheter when considered necessary usually 2–6 l/min. However if treatment with digoxin, isoproterenol, glucagon, beta adrenergic blocking agents, or verapamil was instituted during the period under study measurement of the ST elevation was discontinued. Should a QRS duration of  $>0.12$  seconds or pericarditis occur then the values of the ST elevation were excluded from this point in the final analysis.

Stethoscopy of the lungs and heart was frequently carried out during the period under study. If stethoscopy suggested congestive heart failure then a chest X ray was

taken. In accordance with clinical arbitrary classification of congestive heart failure in patients with AMI (2) 2 patients had no signs of cardiac failure, 25 patients had mild to moderate heart failure, with rales of both lung fields of 50 per cent or less, and 3 had pulmonary oedema with rales over more than 50 per cent of both lung fields. No patients suffered from cardiogenic shock.

All the patients complained of retrosternal pain for more than 20 minutes. Based on this and also on the daily routine recordings of an ECG with 12 leads (I—III, aVR, aVL, aVF, V<sub>1</sub>—V<sub>6</sub>) together with the daily determination of creatine kinase, aspartate aminotransferase, and lactate dehydrogenase in the serum, a definite diagnosis of AMI was made according to the criteria of WHO (16). Fourteen patients had anterior infarction, whereas 16 had inferior infarction.

### 2 ECG recording and measurement

In patients where the initial ECG recording showed an ST elevation  $\geq 2$  mm in V<sub>1</sub>—V<sub>6</sub>, 42 sites were marked on the front of the chest. These sites were obtained by the crossing of 6 horizontal lines and 7 vertical lines. The horizontal lines were fixed by permitting line A to cut IC II at the sternum and line B, IC III at the sternum. The vertical distance between lines A and B was measured, and was used for the positioning of lines C, D, E, and F in a distal sequence. With regard to the vertical lines, lines 1 and 2 were drawn along the right and left sternal borders, respectively and lines 6 and 7 in the left anterior and middle axillary line, respectively. Lines 3, 4 and 5 were obtained by dividing the distance from lines 2 to 6 by four. An ECG was recorded at these 42 sites and an electrode (Red Dot silver/silver chloride) attached to the chest at the site with the highest ST elevation. An ECG was then recorded using this electrode, every hour for the next 48 hours.

In patients where the initial ECG recording showed the highest ST elevation in III and aVF ( $\geq 1$  mm) ECG recordings were made every hour for the next 48 hours using

the lead aVF. All the ECG recordings were made with the patient in the supine position.

The electrocardiograph was a Siemens Elema Mingograph 34 with a paper speed of 50 mm/sec and calibrated to 1 mV=10 mm. The ECG complex was analysed by means of Hewlett Packard 9864A digitizer/9810A calculator. The digitizer consists of three elements: a platen with a digitizing surface, a free moving cursor and a main frame. It enters co-ordinate data from graphic records into a calculator. The duration of the QRS complex and the height of the ST segment 0.06 seconds after the peak of the last wave (usually the S wave in the QRS complex), were calculated with 3 consecutive ECG complexes using these 3 adjacent intervals, we calculated the heart rate as the harmonic mean. The PQ level was used as the base line.

The blood pressure and respiratory rate were measured at the same time as the ECG was recorded. The blood pressure was measured indirectly with a cuff sphygmomanometer and read to the nearest 5 mm Hg.

### 3 The control group

Twenty-five patients comprised the control group of these, 20 were admitted for chest pain but with no indication of AMI and 5 because of extracardiac disease. The average age of the control patients was 49 years, there were 18 men and 7 women. The final diagnoses of these patients were pneumonia 5, ischaemic heart disease 4 (no retrosternal pain or discomfort during the period under study), intercostal muscle myositis 3, diabetes mellitus 2, cholelithiasis 2, lipothymia 2, etc. other patients had no definite diagnosis. The remaining 5 patients suffered from coronary cordis, arterial hypertension, influenza, migraine, and an electric accident, respectively. An ECG was recorded every hour in each of these patients, but for 24 hours only as described in the paragraph on the patient group. Fifteen patients comprised the control group for the patients suffering from anterior infarction, and the ECG was recorded from a precordial lead corresponding to V<sub>4</sub>, I the remaining 10 control patients for those with

an inferior infarction the aVF lead was employed for the recording.

### 4 Reliability of the measurements

The precision of the measurement of length on the scale of the digitizer was checked by measuring a 5 cm length twenty times leaving the paper in the same position on the platen throughout, and then for further twenty times, but removing and replacing the paper between each measurement.

The intra-observer variation in the measurement of the ST deviation by means of the digitizer was studied by twice measuring twenty ST deviations, registered in a precordial lead from the same patient with anterior AMI, at an interval of 24 hours.

The inter-observer variation in the measurement of the ST deviation was also studied by having another person (using the same digitizer) measuring the same twenty ST deviations.

The influence of the electrocardiograph on the measurement of the ST deviation, was studied by means of two Mingographs 34. An ECG was recorded by both instruments, one immediately after the other using a precordial lead on 10 patients. The examination was repeated on each patient.

The influence of different patient positions on ST deviation was evaluated by ECG recordings immediately following each other with the patient first in the left oblique position, second in the supine position, and finally in the right oblique position. This procedure was repeated with each patient, an ECG recording being made via precordial lead thus was carried out on 10 patients (6 controls and 4 with anterior AMI).

### 5 Statistical analysis

The formula  $PSD^2 =$

$$\sim \sum_{i=1}^k \frac{d_i^2}{n} \times \frac{1}{SD^2} \quad \text{was used}$$
$$\sum_{i=1}^k \frac{1}{n}$$

for the calculation of the pooled variance of ST deviations in the control group and also for the calculation of the total pooled variance when evaluating the precision of the



of this method when used for the bedside estimate of ischaemic injury (11-15).

These studies suggest that there is a considerable variability of the ST deviation after AMI. Therefore, in an attempt to elucidate this problem, we have studied the ST elevation from hour to hour in a single surface lead for the first 2 days after admission of patients with AMI and have related the ST elevation to ST deviations measured hourly in patients without AMI. In addition, the ST elevations in patients with AMI have been related to heart rate, blood pressure, respiratory rate, retrosternal pain and oxygen treatment. Clinical factors that can be associated with, or can influence, myocardial ischaemia.

## Material and method

### 1 The patient group

The investigation includes 30 patients with AMI admitted to the coronary care unit (CCU) of the Odense University hospital on average, 2 hours after the onset of symptoms. Their average age was 63 years. There were 22 men and 8 women. Patients with pericarditis, disturbances of electrolyte balance, a QRS duration  $\geq 0.12$  seconds, or patients under drug therapy possibly affecting the ST segment (digitalis, isoproterenol, beta-adrenergic blocking drugs) were not admitted to the study.

The patients were treated according to the usual procedure of the CCU, i.e. rest in bed, morphine, anti-arrhythmic drugs, and diuretics as required, and oxygen via a nasal catheter when considered necessary usually 2-6 l/min. However if treatment with digoxin, isoproterenol, glucagon, beta-adrenergic blocking agents, or verapamil was instituted during the period under study measurement of the ST elevation was discontinued. Should a QRS duration of  $>0.12$  seconds or pericarditis occur then the values of the ST elevation were excluded from this point in the final analysis.

Stethoscopy of the lungs and heart was frequently carried out during the period under study. If stethoscopy suggested congestive heart failure, then a chest X-ray was

taken. In accordance with clinical arbitrary classification of congestive heart failure in patients with AMI (2) 2 patients had no signs of cardiac failure, 25 patients had mild to moderate heart failure, with rales of both lung fields of 50 per cent or less, and 3 had pulmonary oedema with rales over more than 50 per cent of both lung fields. No patients suffered from cardiogenic shock.

All the patients complained of retrosternal pain for more than 20 minutes. Based on this and also on the daily routine recordings of an ECG with 12 leads (I-III, aVR, aVL, aVF,  $V_1-V_6$ ) together with the daily determination of creatine kinase, aspartate aminotransferase, and lactate dehydrogenase in the serum, a definite diagnosis of AMI was made according to the criteria of WHO (16). Fourteen patients had anterior infarction, whereas 16 had inferior infarction.

### 2 ECG recording and measurement

In patients where the initial ECG recording showed an ST elevation  $\geq 2$  mm in  $V_1-V_6$ , 42 sites were marked on the front of the chest. These sites were obtained by the crossing of 6 horizontal lines and 7 vertical lines. The horizontal lines were fixed by permitting line A to cut IC II at the sternum and line B, IC III at the sternum. The vertical distance between lines A and B was measured, and was used for the positioning of lines C, D, E, and F in a distal sequence. With regard to the vertical lines, lines 1 and 2 were drawn along the right and left sternal borders, respectively and lines 6 and 7 in the left anterior and middle axillary line, respectively. Lines 3, 4 and 5 were obtained by dividing the distance from lines 2 to 6 by four. An ECG was recorded at these 42 sites and an electrode (Red Dot silver/silver chloride) attached to the chest at the site with the highest ST elevation. An ECG was then recorded using this electrode, every hour for the next 48 hours.

In patients where the initial ECG recording showed the highest ST elevation in III and aVF ( $\geq 1$  mm) ECG recordings were made every hour for the next 48 hours using

the lead aVF. All the ECG recordings were made with the patient in the supine position.

The electrocardiograph was a Siemens-Elma Mingograph 34 with a paper speed of 50 mm/sec and calibrated to 1 mV = 10 mm. The ECG complex was analysed by means of a Hewlett Packard 9864A digitizer/9810A calculator. The digitizer consists of three elements: platen with a digitizing surface, free moving cursor and a main frame; it enters co-ordinate data from graphic records into a calculator. The duration of the QRS complex and the height of the ST segment 0.06 seconds after the peak of the last wave (usually the S wave in the QRS complex), were calculated with 3 consecutive ECG complexes, using these 3 adjacent intervals, we calculated the heart rate as the harmonic mean. The PQ level was used as the base line.

The blood pressure and respiratory rate were measured at the same time as the ECG was recorded. The blood pressure was measured indirectly with cuff sphygmomanometer and read to the nearest 5 mm Hg.

### 3 The control group

Twenty-five patients comprised the control group of these, 20 were admitted for chest pain but with no indication of AMI, and 5 because of extracardiac disease. The average age of the control patients was 49 years, there were 18 men and 7 women. The final diagnoses of these patients were pneumonia 5 ischaemic heart disease 4 (no retrosternal pain or discomfort during the period under study) intercostal muscle myositis 3 diabetes mellitus 2, cholelithiasis 2, lipothymia 2 two other patients had no definite diagnosis the remaining 5 patients suffered from neuron cordis, arterial hypertension, influenza, migraine, and an electric accident, respectively. An ECG was recorded every hour in each of these patients, but for 24 hours only as described in the paragraph on the patient group. Fifteen patients comprised the control group for the patients suffering from anterior infarction, and the ECG was recorded from precordial lead corresponding to  $V_4$ . In the remaining 10 control patients for those with

an inferior infarction the aVF lead was employed for the recording.

### 4 Reliability of the measurements

The precision of the measurement of length in the use of the digitizer was checked by measuring a 5 cm length twenty times leaving the paper in the same position on the platen throughout, and then for a further twenty times, but removing and replacing the paper between each measurement.

The inter-observer variation in the measurement of the ST deviation by means of the digitizer was studied by twice measuring twenty ST deviations, registered in a precordial lead from the same patient with anterior AMI, at an interval of 24 hours.

The inter-observer variation in the measurement of the ST deviation was also studied by having another person (using the same digitizer) measuring the same twenty ST deviations.

The influence of the electrocardiograph on the measurement of the ST deviation, was studied by means of two Mingographs 34. An ECG was recorded by both instruments, one immediately after the other using a precordial lead on 10 patients. The examination was repeated on each patient.

The influence of different patient positions on ST deviation was evaluated by ECG recordings immediately following each other with the patient first in the left oblique position, second in the supine position, and finally in the right oblique position. This procedure was repeated with each patient, an ECG recording being made via precordial lead this was carried out on 10 patients (6 controls and 4 with anterior AMI).

### 5 Statistical analysis

The formula  $PSD^2 =$

$$\sum_{i=1}^k \frac{d_i^2}{n} \times SD^2 \quad \text{was used}$$
$$\sum_{i=1}^k \frac{d_i^2}{n}$$

for the calculation of the pooled variance of ST deviations in the control group and also for the calculation of the total pooled variance when evaluating the precision of the

of this method when used for the bedside estimate of ischaemic injury (11-15)

These studies suggest that there is a considerable variability of the ST deviation after AMI. Therefore, in an attempt to elucidate this problem, we have studied the ST elevation from hour to hour in a single surface lead for the first 2 days after admission of patients with AMI and have related the ST elevation to ST deviations measured hourly in patients without AMI. In addition, the ST elevations in patients with AMI have been related to heart rate, blood pressure, respiratory rate, retrosternal pain and oxygen treatment, clinical factors that can be associated with, or can influence, myocardial ischaemia.

## Material and method

### 1 The patient group

The investigation includes 30 patients with AMI admitted to the coronary care unit (CCU) of the Odense University hospital on average 2 hours after the onset of symptoms. Their average age was 63 years. There were 22 men and 8 women. Patients with pericarditis, disturbances of electrolyte balance, a QRS duration  $\geq 0.12$  seconds, or patients under drug therapy possibly affecting the ST segment (digitalis, isoproterenol, beta adrenergic blocking drugs) were not admitted to the study.

The patients were treated according to the usual procedure of the CCU, i.e. rest in bed, morphine, anti arrhythmic drugs, and diuretics as required, and oxygen via a nasal catheter when considered necessary, usually 2-6 l/min. However if treatment with digoxin, isoproterenol, glucagon, beta adrenergic blocking agents, or verapamil was instituted during the period under study, measurement of the ST elevation was discontinued. Should a QRS duration of  $>0.12$  seconds or pericarditis occur, then the values of the ST elevation were excluded from this point in the final analysis.

Stethoscopy of the lungs and heart was frequently carried out during the period under study. If stethoscopy suggested congestive heart failure, then a chest X ray was

taken. In accordance with clinical arbitrary classification of congestive heart failure in patients with AMI (2), 2 patients had no signs of cardiac failure, 25 patients had mild to moderate heart failure, with rales of both lung fields of 50 per cent or less, and 3 had pulmonary oedema with rales over more than 50 per cent of both lung fields. No patients suffered from cardiogenic shock.

All the patients complained of retrosternal pain for more than 20 minutes. Based on this and also on the daily routine recordings of an ECG with 12 leads (I-III, aVR, aVL, aVF, V<sub>1</sub>-V<sub>6</sub>) together with the daily determination of creatine kinase, aspartate aminotransferase, and lactate dehydrogenase in the serum, a definite diagnosis of AMI was made according to the criteria of WHO (16). Fourteen patients had anterior infarction, whereas 16 had inferior infarction.

### 2 ECG recording and measurement

In patients where the initial ECG recording showed an ST elevation  $\geq 2$  mm in V<sub>1</sub>-V<sub>6</sub>, 42 sites were marked on the front of the chest. These sites were obtained by the crossing of 6 horizontal lines and 7 vertical lines. The horizontal lines were fixed by permitting line A to cut IC II at the sternum and line B IC III at the sternum. The vertical distance between lines A and B was measured, and was used for the positioning of lines C, D, E, and F in a distal sequence. With regard to the vertical lines, lines 1 and 2 were drawn along the right and left sternal borders, respectively, and lines 6 and 7 in the left anterior and middle axillary line, respectively. Lines 3, 4 and 5 were obtained by dividing the distance from lines 2 to 6 by four. An ECG was recorded at these 4 sites and an electrode (Red Dot silver/silver chloride) attached to the chest at the site with the highest ST elevation. An ECG was then recorded, using this electrode, every hour for the next 48 hours.

In patients where the initial ECG recording showed the highest ST elevation in III and aVF ( $\geq 1$  mm) ECG recordings were made every hour for the next 48 hours using

precordial lead was attached. In all the patients, the initial highest ST elevation was measured in the antero-septal area. The first measurement of the ST elevation was carried out  $357 \pm 47$  minutes (mean  $\pm$  SEM; range 150–610 min) after the onset of the infarction. The table also shows the variance of the hourly measurements of the ST elevations in each individual patient. A comparison was made between these values and the pooled variance of the ST deviation of the control group in order to evaluate the inter-individual variation, and by means of a F-test, it was found that 13 of the 14 patients had a significantly increased variance in relation to the patients of the control group. Patients Nos. 3, 8 and 33 died, 91, 10, and 41 hours, respectively after the onset of symptoms. Thirteen measurements of the ST elevation only are given in the table for patient No. 12, the reason for this being that the patient developed a QRS  $> 0.12$  seconds.

The first measurement of ST elevation in lead aVF was carried out  $195 \pm 21$  minutes

(mean  $\pm$  SEM range 30–355 min) after the onset of symptoms in 16 patients with inferior AMI. With a F-test comparison of the individual patient's variance of the hourly ST elevation, with the pooled variance of the ST deviation of the 10 control patients, showed that 13 of the 16 patients had a significantly increased variance. In patient No. 10, only 6 measurements of the ST elevation were carried out, this patient was given digoxin treatment. Owing to pacemaker treatment, patient No. 36 was only subjected to 9 measurements of the ST elevation.

In order to evaluate the inter-individual variation, the hourly measurements of the ST elevation were related to time following the onset of symptoms. Table III shows that, with anterior AMI, 6 patients had a significantly positive correlation between ST elevation and time, whereas the correlation was significantly negative in 5 patients. From table IV it can be seen that with inferior AMI, 3 and 7 patients had positive and negative correlation, respectively between ST elevation and time.

Tables III and IV show the measured ST elevations related to the simultaneously measured heart rate. With anterior AMI, 5 patients had a significantly positive correlation between ST elevation and heart rate; in addition, these patients' ST elevation was positively correlated to time. The 14 patients, with anterior AMI had significantly higher heart rate than the 15 control patients, on average 91 and 68 respectively ( $p < 0.001$ ). There was no difference in the heart rate of the 5 patients with significantly positive correlation between ST elevation and heart rate and the other 9 patients. In patients with inferior AMI there were 3 patients with a significantly positive correlation between ST elevation and heart rate, but there was no correlation in the remaining patients. Heart rate in patients with inferior AMI did not differ significantly from the heart rate of the control patients nor was there any difference in the heart rate of the 3 patients with positive correlation to the ST elevation and the remaining 13 patients.

Table II Electrode position and inter-individual variation of ST elevation in patients suffering from anterior AMI

Case No.	Electrode position	N of measurements	Variance of ST elevation (Pooled SEM)	Significance
3	C3	8	0.303	$P < 0.01$
5	C2	48	4.068	$P < 0.01$
7	E3	50	0.978	$P < 0.01$
8	E3	5	0.373	$P < 0.01$
11	D2	48	0.279	$P < 0.01$
12	D2	13	1.435	$P < 0.01$
14	E2	51	0.063	n.s.
21	C3	49	0.995	$P < 0.01$
22	D	51	0.243	$P < 0.01$
23	C3	57	0.353	$P < 0.01$
29	C2	48	0.813	$P < 0.01$
31	C2	50	0.741	$P < 0.01$
33	C3	36	0.608	$P < 0.01$
37	D3	50	0.116	$P < 0.01$

The pooled variance is from 15 control patients

method using several measuring series PSD = pooled standard deviation.  $k$  = the number of samples,  $df_1$  and  $SD_1^2$  are the degrees of freedom ( $n_1 - 1$ ) and the variance in sample 1. PSD on double determinations was calculated according to the formula  $PSD^2 =$

$$\frac{1}{2k} \sum_{i=1}^k d^2 \text{ where } d = \text{the difference}$$

between 2 double determinations. The comparison of several correlation coefficients ( $r$ ) was effected by means of the test statistic

$$2 \sum_{i=1}^k (n-3) (z_i - \bar{z})^2 \text{ as the distribution}$$

of the sample correlation coefficients can be normalized approximately by means of

$$\text{Fisher's } z \text{ transformation } z = \frac{1}{2} \ln \frac{1+r}{1-r}$$

$$\text{and } r = \frac{e^2 - 1}{e^2 + 1} \text{ significance limit for } X^2$$

distribution (3). Otherwise  $t$  test and  $F$ -test were employed. A significance level of 0.05 was chosen.

## Results

### Reliability of ST deviation measurement

The measurement of a set length by means of the digitizer gave an  $SD = 0.06$  mm. With a change in the position of the paper between each measurement, the  $SD$  was 0.09 mm.

The inter and intra-observer variation in the measurement of the ST deviation constituted a PSD of 0.16 mm and 0.18 mm respectively. The measurement of the ST deviation with different electrocardiographs, produced a PSD of 0.15 mm.

Table I shows the influence that the position of the patient had on the ST deviations when these were registered via a precordial lead. Between the normal supine position and a left or right oblique position, the PSD was 0.24 mm and 0.21 mm respectively. A  $F$  test showed that the measured PSDs of the variation in positioning of the patients did not differ significantly from the measuring error.

The pooled variance and PSD of the measured ST deviations, taken every hour

Table I The influence of posture on the ST segment in a precordial lead.

Case no	ST deviation (mm)		
	Left oblique position	Supine position	Right oblique position
21	4.0	3.9	3.4
	4.9	4.5	3.9
22	3.0	4.0	4.0
	4.0	4.2	4.3
23	1.8	1.9	2.1
	1.3	0.7	0.1
24	0.3	0.1	0.4
	0.6	0.9	0.7
25	1.9	2.0	2.0
	1.9	2.2	2.2
27	0.3	0.4	0.5
	0.4	0.4	0.4
28	0.4	0.4	0.1
	0.8	0.6	0.1
29	3.8	3.8	3.9
	3.9	3.4	3.6
30	3.2	3.1	3.0
	3.5	3.1	3.3
32	1.7	1.9	1.7
	1.8	1.6	1.9
PSD	0.24 mm	0.21 mm	

were 0.067 and 0.26 mm, respectively after recording via a precordial lead in 15 control patients, and 0.031 and 0.18 mm using aVF in 10 control patients. A  $F$  test showed that  $PSD = 0.26$  mm in the first control group was significantly greater than the PSD of 0.18 mm ( $p < 0.05$ ) for the measuring error but not significantly different from the PSDs of 0.24 mm and 0.21 mm for the variation in the position of the patient. A  $PSD = 0.18$  mm in the other control group corresponds to the PSD of the measuring error.

### Patients with AMI

Table II shows the numbers of the 14 patients who suffered from anterior AMI. The capital letter followed by a figure indicates the position of the electrode to which the

51c IV Correlation between ST elevation and time after onset of symptoms. Heart rate, mean arterial blood pressure, heart rate x systolic blood pressure and respiratory rate in patients differing from inferior AMI

Case no.	Type	Heart rate			Mean arterial B.P.			Heart rate x systolic B.P.			Respiratory rate				
		r	p	n	r	p	n	r	p	n	r	p	n		
	-0.807	51	<0.001	0.236	51	n.s.	0.521	50	<0.001	0.468	50	<0.001	-0.373	49	<0.01
6	-0.023	41	n.s.	0.250	41	n.s.	0.225	38	n.s.	0.495	38	n.s.	0.173	39	n.s.
9	0.088	26	n.s.	0.063	26	n.s.	0.304	26	n.s.	0.316	6	n.s.	0.144	23	n.s.
10	-0.42	6	n.s.	-0.113	6	n.s.	0.424	5	n.s.	0.314	6	n.s.	0.318	4	n.s.
34	-0.720	5	<0.001	0.244	52	n.s.	0.234	48	n.s.	0.486	48	<0.001	-0.269	47	n.s.
36	0.695	9	<0.05	0.873	9	<0.01	0.910	6	<0.05	0.934	8	<0.001	-0.809	6	n.s.
41	0.364	49	<0.05	0.076	49	n.s.	-0.210	47	n.s.	-0.036	47	n.s.	0.005	47	n.s.
42	-0.196	29	n.s.	0.040	29	n.s.	0.410	27	<0.05	0.277	27	n.s.	-0.211	26	n.s.
43	-0.736	33	<0.001	0.331	33	n.s.	0.810	31	<0.001	0.659	33	<0.001	0.191	33	n.s.
46	0.113	51	n.s.	0.197	51	n.s.	-0.144	49	n.s.	0.166	49	n.s.	0.043	49	n.s.
47	-0.882	55	<0.001	-0.137	55	n.s.	0.477	55	<0.001	-0.061	55	n.s.	-0.242	55	n.s.
49	-0.353	54	<0.01	0.410	54	<0.001	0.71	50	<0.001	0.857	50	<0.001	0.118	50	n.s.
51	-0.418	53	<0.01	-0.118	53	n.s.	-0.005	51	n.s.	-0.069	51	n.s.	-0.164	49	n.s.
55	-0.087	49	n.s.	0.069	49	n.s.	-0.017	48	n.s.	0.072	48	n.s.	0.157	48	n.s.
56	-0.575	44	<0.001	-0.263	44	n.s.	0.693	43	<0.001	0.681	43	<0.001	-0.372	43	<0.001
58	0.339	58	<0.05	0.402	50	<0.01	-0.181	49	n.s.	0.242	49	n.s.	-0.070	49	n.s.
X <sup>2</sup> distribution of r		194.084	50.284		99.685	96.775		35.364		p<0.0005		p<0.005			
df=15		p<0.0005		p<0.0005		p<0.0005		p<0.0005		p<0.0005		p<0.005			

Table III  
Correlation between ST elevation and time after onset of symptoms heart rate mean arterial blood pressure heart rate x systolic blood pressure and respiratory rate in patients suffering from anterior AMI

Case no	Time			Heart rate			Mean arterial BP			Heart rate x systolic B.P			Respiratory rate		
	r	n	p	r	n	p	r	n	p	r	n	p	r	n	p
3	-0.642	8	n.s.	-0.453	8	n.s.	-0.491	8	n.s.	-0.492	8	n.s.	-0.550	7	n.s.
5	0.710	48	<0.001	0.760	48	<0.001	-0.137	47	n.s.	0.475	47	<0.001	0.614	47	<0.001
7	0.768	50	<0.001	0.800	50	<0.001	-0.243	50	n.s.	0.635	50	<0.001	-0.218	49	n.s.
8	-0.992	5	<0.001	-0.392	5	n.s.	0.954	4	<0.05	0.991	4	<0.01	-0.518	4	n.s.
11	0.702	48	<0.001	0.578	48	<0.001	-0.315	48	<0.05	0.219	48	n.s.	0.415	46	<0.01
12	-0.330	13	n.s.	0.426	13	n.s.	0.569	13	<0.05	0.491	13	n.s.	0.400	13	n.s.
14	-0.376	51	<0.01	0.008	51	n.s.	-0.080	48	n.s.	0.135	48	n.s.	-0.017	48	n.s.
21	-0.462	49	<0.001	0.030	49	n.s.	0.344	46	<0.05	0.404	46	<0.01	0.302	45	<0.05
22	0.625	51	<0.001	-0.277	51	<0.05	-0.321	47	<0.05	-0.387	47	<0.01	-0.035	47	n.s.
23	-0.627	57	<0.001	-0.045	57	n.s.	0.527	50	<0.001	0.444	50	<0.001	0.219	46	n.s.
29	0.811	48	<0.001	0.701	48	<0.001	-0.003	44	n.s.	0.524	44	<0.001	0.711	39	<0.001
31	0.709	50	<0.001	0.861	50	<0.001	-0.016	49	n.s.	0.549	49	<0.001	0.332	48	<0.05
33	-0.673	36	<0.001	-0.084	36	n.s.	-0.341	33	n.s.	-0.550	36	<0.001	0.056	36	n.s.
37	-0.260	50	n.s.	0.014	50	n.s.	-0.306	39	n.s.	0.044	39	n.s.	-0.138	38	n.s.
Y's distribution of r															
df=13	303.408			156.593			50.584			84.998			53.680		
	p<0.0005			p<0.0005			p<0.0005			p<0.0005			p<0.0005		

Table 11. Correlation between ST elevation and time after onset of symptoms. heart rate, mean arterial blood pressure, heart rate x systolic blood pressure and respiratory rate in patients suffering from inferior AMI

No.	Time		Heart rate		Mean arterial B.P.		Heart rate x systolic B.P.		Respiratory rate	
	P	n	P	n	P	n	P	n	P	n
2	0.807	51	<0.001	51	n.s.	50	<0.001	50	0.373	49
6	0.023	41	n.s.	41	n.s.	38	n.s.	38	0.173	39
9	0.088	26	n.s.	26	n.s.	26	n.s.	26	0.144	23
10	0.427	6	n.s.	6	n.s.	5	n.s.	6	0.318	4
34	0.770	52	<0.001	52	n.s.	48	<0.001	48	0.269	47
36	0.695	9	<0.05	9	<0.01	6	<0.05	8	0.809	6
41	0.364	49	<0.05	49	n.s.	47	n.s.	47	0.005	47
42	0.196	29	n.s.	29	n.s.	27	<0.05	27	0.211	26
43	0.756	33	<0.001	33	n.s.	31	<0.001	33	0.191	33
46	0.113	51	n.s.	51	n.s.	49	n.s.	49	0.043	49
47	0.882	55	<0.001	55	n.s.	55	<0.001	55	0.242	55
49	0.353	54	<0.01	54	<0.001	50	<0.001	50	0.118	50
51	0.418	53	<0.01	53	n.s.	51	n.s.	51	0.164	49
55	0.087	49	n.s.	49	n.s.	48	n.s.	48	0.157	48
56	0.573	44	<0.001	44	n.s.	43	<0.001	43	0.372	43
58	0.339	50	<0.05	50	<0.01	49	n.s.	49	0.070	49

X<sup>2</sup> distribution of r df=15 194.084 P<0.0005 99.683 P<0.0005 96.775 P<0.0005 35.564 P<0.005



The ST elevation is also related to mean arterial blood pressure in Tables III and IV. With anterior AMI there was positive correlation between these variables in 4 patients and negative correlation in 2 patients. With inferior AMI there was positive correlation between these variables in 7 patients, but correlation was absent in 9 patients.

Tables III and IV show the relation between ST elevation and the product of heart rate and systolic blood pressure. With anterior AMI 7 patients had a positive correlation between these variables and 4 patients also had a positive correlation between ST elevation and heart rate; the remaining 3 patients had a positive correlation between ST elevation and mean arterial blood pressure. With inferior AMI 6 patients had a positive correlation between ST elevation and heart rate multiplied by systolic blood pressure; of these, 5 and 2 patients also had a positive correlation between ST elevation and mean arterial blood pressure, and ST elevation and heart rate respectively.

Tables III and IV also show the relation between ST elevation and respiratory rate. With anterior AMI there was a positive correlation between these variables in 5 patients whereas in the patients with inferior AMI there was no correlation, apart from 2 patients with negative correlation.

Tables III and IV also show the  $X^2$  distribution of the correlation coefficients following a transformation. In each group the  $X^2$  is far greater than the chosen confidence limits as an expression of a very large dispersion of the correlation coefficients within the individual groups.

The presence of retrosternal pain or chest discomfort was registered based on information supplied by the patients. Comparisons were made with the paired  $t$  test between the measured ST elevation in patients with anterior AMI partly before and after the pain caused. In neither case was it possible to demonstrate that the pain had any influence on ST elevation.

Patients with anterior AMI were studied for the influence of nasal oxygen therapy on

ST elevation. A comparison between the measured ST elevations before and after the administration of oxygen, and before and after the cessation of oxygen therapy respectively showed that oxygen treatment had no influence on ST elevation.

## Discussion

In the present study the ST segment elevation during the early phase of AMI was followed in a single unipolar lead in anterior infarctions, the precordial lead giving the highest initial ST elevation was used, whereas in patients with inferior AMI the aVF lead was employed.

Our data of the reliability of the method showed that the variations of ST segment deviations in the control groups were of the same magnitude as the measuring error. When the aVF lead was used the variation corresponded to the measuring error whereas use of a precordial lead produced a significantly greater variation of the ST deviations than that corresponding to the measuring error but the variations were not significantly greater than the total measuring error of the method, which included patient positioning.

The investigation showed that the spontaneous course of hourly measurements of ST elevations for 48 hours after the onset of the infarction is marked by a pronounced variability. This applied both to anterior and inferior infarction. The intraindividual variation of the ST elevations in patients with AMI was significantly greater than in the control patients. The inter individual variation of the ST elevation in patients with AMI was also statistically significant. The explanation which immediately suggests itself is that this pronounced variability of the ST elevations can be due to a corresponding variability in the clinical parameters as these influence or could have some connection with, the myocardial ischaemia, for instance oxygen treatment, retrosternal pain, heart rate, blood pressure or respiratory rate.

Arterial hypoxaemia is common during the first few days after AMI (2) and it has

been demonstrated experimentally that hypotension increases ischaemic injury after coronary occlusion (12). It has also been found that enrichment of inspired oxygen content reduced ST elevation as recorded in precordial mapping in human AMI (7). In our investigation, nasal oxygen therapy had no influence on ST elevation in patients with anterior AMI, but it is possible that the administration of an oxygen flow of 2-6 l/min is too low to influence myocardial ischaemia.

Precordial ST segment mapping technique has shown that attacks of cardiac pain result in an increased ST elevation (9). However, in the present study the commencement and cessation of retrosternal pain or chest discomfort had no influence on the hourly measured ST elevations in patients with anterior AMI, although we had the impression that the information on chest discomfort obtained from the patients was imprecise in several cases. In this connection, the patient's pain threshold is of considerable importance.

The fact that increased heart rate also increases ischaemic damage has been demonstrated in experimental studies (8, 13). A similar observation has been reported in patients (14). In our investigation, a significant positive correlation could only be demonstrated between ST elevation and heart rate in fewer patients, but this was perhaps due to the heart rate mainly falling within normal limits, where changes in myocardial oxygen consumption are possibly too small to cause significant alteration in the ST segment.

The reduction in arterial blood pressure decreases myocardial wall tension and lowers myocardial oxygen requirements. If there is concomitant severe decrease in coronary perfusion pressure, there is a tendency for the myocardial oxygen delivery to the ischaemic areas to be diminished also, and therefore to interfere with the beneficial effect on ischaemia obtained from the decrease in myocardial oxygen requirement (8, 13). These two contrary effects of lowering arterial blood pressure can possibly be the cause of the investigation not demonstrating any pattern of

the correlation coefficients between ST elevation and mean arterial blood pressure.

The product of heart rate and systolic blood pressure has been employed clinically as a reasonable indirect measure of the oxygen consumption of the myocardium (6). In patients with AMI a rising product should thus result in a rising ST elevation. In the present study significant positive correlation could be demonstrated between ST elevation and heart rate multiplied by systolic blood pressure in almost one half of the patients.

When pulmonary disease can be excluded in patients with AMI increased respiratory rate indicates the presence of cardiac insufficiency which is usually related to the extent of the injured myocardium (2, 10). In the present investigation, 93 % of the patients had heart failure despite this, only 36 % of the patients with anterior AMI had positive correlation between respiratory rate and ST elevation; in patients with inferior AMI there was no positive correlation between these variables.

Our results thus suggest that, in part, there was significant dispersion of the correlation coefficients within the individual groups in which a correlation was made between ST elevation and heart rate, mean arterial blood pressure, heart rate multiplied by systolic blood pressure, and respiratory rate, respectively and partly that the correlation coefficients were variable between the different groups. Thus the variability of the ST elevations was most often inexplicable and only rarely attributable to alterations in the clinical status. There can be several causes of this inconsistent correlation. On the one hand, it is possible that the clinical variables are poorly correlated to myocardial ischaemia when these variables mainly lie within normal ranges; this is in contrast to experimental conditions where the heart rate and blood pressure are artificially provoked to extreme values (8, 13) with a subsequently greater influence on myocardial oxygen consumption. On the other hand, factors other than ischaemia might affect the ST segment, i.e. change in pH and ion concentrations, temperature changes, or sympathetic stimulation of

The ST elevation is also related to mean arterial blood pressure in Tables III and IV. With anterior AMI, there was positive correlation between these variables in 4 patients and negative correlation in 2 patients. With inferior AMI there was positive correlation between these variables in 7 patients, but correlation was absent in 9 patients.

Tables III and IV show the relation between ST elevation and the product of heart rate and systolic blood pressure. With anterior AMI 7 patients had a positive correlation between these variables and 4 patients also had a positive correlation between ST elevation and heart rate; the remaining 3 patients had a positive correlation between ST elevation and mean arterial blood pressure. With inferior AMI 6 patients had a positive correlation between ST elevation and heart rate multiplied by systolic blood pressure; of these, 5 and 2 patients also had a positive correlation between ST elevation and mean arterial blood pressure, and ST elevation and heart rate, respectively.

Tables III and IV also show the relation between ST elevation and respiratory rate. With anterior AMI there was a positive correlation between these variables in 5 patients, whereas in the patients with inferior AMI there was no correlation, apart from 2 patients with negative correlation.

Tables III and IV also show the  $\chi^2$  distribution of the correlation coefficients following  $z$  transformation. In each group the  $\chi^2$  is far greater than the chosen confidence limits as an expression of a very large dispersion of the correlation coefficients within the individual groups.

The presence of retrosternal pain or chest discomfort was registered, based on information supplied by the patients. Comparisons were made with the paired  $t$ -test between the measured ST elevation in patients with anterior AMI partly before and after the pain caused. In neither case was it possible to demonstrate that the pain had any influence on ST elevation.

Patients with anterior AMI were studied for the influence of nasal oxygen therapy on

ST elevation. A comparison between the measured ST elevations before and after the administration of oxygen, and before and after the cessation of oxygen therapy respectively showed that oxygen treatment had no influence on ST elevation.

## Discussion

In the present study the ST segment elevation during the early phase of AMI was followed in a single unipolar lead in anterior infarctions, the precordial lead giving the highest initial ST elevation was used, whereas in patients with inferior AMI the aVF lead was employed.

Our data of the reliability of the method showed that the variations of ST segment deviations in the control groups were of the same magnitude as the measuring error. When the aVF lead was used the variation corresponded to the measuring error; whereas use of a precordial lead produced a significantly greater variation of the ST deviations than that corresponding to the measuring error, but the variations were not significantly greater than the total measuring error of the method, which included patient positioning.

The investigation showed that the spontaneous course of hourly measurements of ST elevations for 48 hours after the onset of the infarction is marked by a pronounced variability. This applied both to anterior and inferior infarction. The intra-individual variation of the ST elevations in patients with AMI was significantly greater than in the control patients. The inter-individual variation of the ST elevation in patients with AMI was also statistically significant. The explanation which immediately suggests itself is that this pronounced variability of the ST elevations can be due to a corresponding variability in the clinical parameters, as these influence or could have some connection with the myocardial ischaemia, for instance oxygen treatment, retrosternal pain, heart rate, blood pressure or respiratory rate.

Arterial hypoxaemia is common during the first few days after AMI (2) and it has

# Rapid monitoring of regional myocardial ischaemia with echocardiography and ST segment shifts in man

Modification of 'Infarct size' and hemodynamics by dopamine and beta blockade

Juhani Heikkilä MD and Markku S Nieminen MD

From the Cardiovascular Laboratory and the Intensive Care Unit, First Department of Medicine, University Central Hospital, HELSINKI FINLAND

Supported by the Paavo Nurmi Foundation and the Finnish Foundation for Cardiovascular Research

## Abstract

A multisensory echocardiographic technique was applied to visualize the mechanical performance of the ischaemic and noninfarcted myocardial segments in 42 patients with acute myocardial infarction. The echo technique was used together with 12 lead electrocardiogram and Swan-Ganz thermodilution to study the immediate effects of graded dopamine infusions and beta blocking drugs on both hemodynamics and infarct size. Twenty patients were studied using dopamine. 11 of them with subsequent 5 mg dose of prazosin. 0.2 mg of pindolol dose was given to 22 patients.

The acute and significant alterations of the ST segment shifts induced by such pharmacological intervention were accompanied by directionally similar changes in the contractile function of the ischaemic myocardial segments ( $p < 0.01$ ). The best agreement was noted between the reduction in the ST segment shifts and the recovery of mechanical function in the ischaemic segments after beta blockade the concordance was 88 % ( $p < 0.01$ ).

Dopamine improved hemodynamic function markedly without arrhythmia ( $p < 0.001$ ). In nonfailing hearts dopamine constantly increased signs of ischaemia, but in 5 of the 11 patients with serious pump failure, dopamine improved circulation without worsening the ST segment ( $p < 0.001$ ). This was probably due to concomitant reduction of the left ventricular diameter ( $p < 0.0005$ ) and thereby of wall stress. The small intravenous dose of 0.2 mg pindolol was hemodynamically safe in the 22 patients with uncomplicated infarction and with moderate left heart failure. Left ventricular filling pressure and stroke volume did not change, nor did any ventricular dilatation take place. The ST segments were improved by 30 % ( $p < 0.0005$ ) and the contractile function of the ischaemic segments improved markedly ( $p < 0.0005$ ) by 25.6 % of the normal, at 15 minutes on average of 15 hours from the onset of symptoms. Prazosin, given subsequent to dopamine and later 25 hours from the onset, also reduced these signs of ischaemia significantly though somewhat less than pindolol.

the heart (1-4). Consequently it would be misleading to suppose that changes in ST elevation during AMI reflect changes in myocardial ischaemia only.

## Acknowledgement

The authors thank both Professor J. Fabricius and Lise Hansen M.Sc. for valuable help.

## References

- 1 Braunwald, E. & Maroko, P. R. ST segment mapping: Realistic and unrealistic expectations. *Circulation* 54: 529-1976.
- 2 Brest, A. N. Heart failure in acute myocardial infarction. In: *Innovations in the diagnosis and management of acute myocardial infarction* (ed. A. N. Brest, L. Wiener, E. K. Chung & H. Kasparian) 245-250. F. A. Davis Company Philadelphia 1975.
- 3 Documenta Geigy: Mathematics and statistics. Ciba-Geigy limited, Basle 1975.
- 4 Fozzard, H. A. & DasGupta, D. S. ST segment potentials and mapping. Theory and experiments. *Circulation* 54: 533-1976.
- 5 Holland, R. P. & Brooks, H. Precordial and epicardial surface potentials during myocardial ischemia in the pig: A theoretical and experimental analysis of the TQ and ST segments. *Circ. Res.* 37: 471-1975.
- 6 Kitamura, K., Jorgensen, C. R., Gobel, F. L., Taylor, H. L., Wang, Y. & Olds, D. P. Hemodynamic correlates of myocardial oxygen consumption during upright exercise. *J. Appl. Physiol.* 32: 516-1972.
- 7 Madias, J. E., Madias, N. L. & Hood, W. H. Jr. Precordial ST segment mapping. 2. Effects of oxygen inhalation on ischemic injury in patients with acute myocardial infarction. *Circulation* 53: 411-1976.
- 8 Maroko, P. R., Hekshus, J. K., Sobel, B. E., Watanabe, T., Covell, J. W., Ross, J. Jr & Braunwald, E. Factors influencing infarct size following experimental coronary artery occlusions. *Circulation* 43: 67-1971.
- 9 Maroko, P. R., Libby, P., Covell, J. W., Sobel, B. E., Ross, J. Jr & Braunwald, E. Precordial S-T segment elevation mapping: An atraumatic method for assessing alterations in the extent of myocardial ischemic injury. The effects of pharmacologic and hemodynamic interventions. *Amer. J. Cardiol.* 29: 223-1972.
- 10 Master, A. M., Dack, S. & Jaffe, H. L. Coronary thrombosis: An investigation of heart failure and other factors in its course and prognosis. *Amer. Heart J.* 13: 330-1937.
- 11 Norris, R. M., Barratt-Boyes, C., Heng, M. K. & Singh, B. N. Failure of ST segment elevation to predict severity of acute myocardial infarction. *Brit. Heart J.* 38: 85-1976.
- 12 Radványi, P., Maroko, P. R. & Braunwald, E. Effects of hypoxemia on the extent of myocardial necrosis after experimental coronary occlusion. *Amer. J. Cardiol.* 35: 795-1975.
- 13 Redwood, D. R., Smith, E. R. & Epstein, S. E. Coronary artery occlusion in the conscious dog: Effects of alterations in heart rate and arterial pressure on the degree of myocardial ischemia. *Circulation* 46: 323-1972.
- 14 Richman, S. Adverse effect of atropine during myocardial infarction. Enhancement of ischemia following intravenously administered atropine. *J. Amer. Med. Ass.* 228: 1414-1974.
- 15 Thompson, P. L. & Katavatos, V. Acute myocardial infarction. Evaluation of precordial ST segment mapping. *Brit. Heart J.* 38: 1020-1976.
- 16 Working group on the establishment of ischaemic heart disease registers. Report of the fifth working group. EURO 8201 (5). World Health Organization, Copenhagen 1971.

*Table 1 Noninvasive Techniques to Evaluate Infarct Size in Man.*

	<i>Time needed</i>
Myocardial enzyme release (CK)	Hours
Radionucleide imaging	Hours to days
ST segment elevation	Minutes
Segmental myocardial function (echo)	Seconds

mechanical dysfunction of the ischaemic myocardium (22, 48, 53, 64). In contrast, the hemodynamic overall pump function remains rather insensitive since it represents team work by both the ischaemic ones and the compensating uninvolved zones (6, 53).

We decided to study functional signs of ischaemia as rapidly as they are shown by ST segment shifts, but more directly. One indicator that can be used in practice for this purpose, though it has not so far been utilized to man, is segmental wall contraction.

This report concentrates mainly on the feasibility of using echocardiography to document the performance of regional myocardial function in acute ischaemia, i.e. both its recovery by beneficial drug intervention as well as its behavior as a rapid indicator of events which increase ischaemia. These direct signs of ischaemia were compared with simultaneous ST segment alterations. Our combined technique of myocardial segment — ST segment mapping seems to be a rewarding clinical tool for rapid directional studies of ischaemic injury.

#### *Relationship between ST segment shifts and ischaemia*

Electrophysiologically ST segment alterations closely reflect myocardial ischaemic injury. Extensive investigations have generally established that acute epicardial and intramural ST segment shifts provide valid, sensitive and reproducible methods for assessing ischaemic injury after experimental coronary occlusion (40, 63) though in the center of a very large injury ST segment elevation may be minimized (4, 20). Thus, ST segment elevation

correlates directly with myocardial oxygen and carbon dioxide tension, anaerobic metabolism, myocardial enzyme depletion, and subsequent light and electron microscopic histology (63). Alterations in the extent of electrocardiographic ischaemic injury are related to changes induced in myocardial oxygen demand and coronary blood flow (20, 26, 48, 63). Surface electrocardiographic ST segment changes at the precordium reflect epicardial electrophysiology extremely closely and consistently (48).

Another important factor is that alterations of reversible myocardial injury as mirrored almost instantaneously in changes in ST segment elevation (48). This relationship and the finding that the ST segment maps are stable in the absence of further myocardial damage (6, 33, 37, 40, 59, 66) permits the use of ST segments as rapid marker of ischaemia for intervention studies in patients with acute myocardial infarction.

However the ST segment shift only directionally with certain reservations (4, 20, 48) indicates the increase or relief of ischaemic injury. Percentual deviations of the initial ST segments are not quantitatively related to the later final mass of the infarct (20, 48, 63). A better prediction of the final infarct size available from electrocardiograms by studying the subsequent development of QRS changes in those leads initially showing ST elevations (3, 39).

Nonischaemic causes of ST segment changes in patients with myocardial infarction are common, including conduction defects pericarditis, electrolyte alterations, drugs and electrode placement (23, 48, 63). These disturbances can be largely voided in the short-term intervention studies where the patients serve as their own controls. Clearly ST segment analysis provides a useful noninvasive clinical tool that can be used to detect acute change in the severity of ischaemic injury at least, over relatively short periods of time (48, 63, 66). The method is rapid, easy to use and directionally accurate.

ST segments in the present study were recorded from the standard 12 leads. The

For rapid characterization of myocardial ischaemia and infarction, the mechanical segmental function of the left ventricle by echo, together with the ST segments, provides an informative clinical method

#### *Wavefront progression of ischaemic cell death a therapeutic challenge*

Acute myocardial infarction is not a sudden permanent loss of myocardium. In autopsy studies of patients dying of acute myocardial infarction tissue damage has often been found to occur in a progressive and scattered manner (2, 7, 12). The vulnerability of the sub-endocardial zones to ischaemia has been convincingly demonstrated (32, 45, 67); this is where the wavefront of the progressive myocardial ischaemia is initiated. In fact, ischaemic myocardial zones of very considerable size (30–50 %) can be salvaged by various types of pharmacological intervention up to six hours following the experimental total coronary artery occlusion (38). Otherwise, many hemodynamic circumstances and types of pharmacological intervention greatly increase the ischaemic injury (22).

In human myocardial infarction, the development of the final infarct size is delayed even more. A stepwise course has been reported biochemically and electrocardiographically in the majority (60 to 80 %) of patients (22, 26, 31, 42, 59). Considerable extensions of the ischaemic damage at the "twilight zones" surrounding the center of the infarct may take place even over a period of several days. Both the short term and late prognoses of the patients after infarction are well known to be determined fundamentally by the extent of the resulting left ventricular dysfunction. Therefore, the new concept of limiting the infarct size (5) is becoming an increasingly important approach in early treatment. At least an inadvertent increase of the evolving infarct induced by certain drugs should be avoided.

#### *Hemodynamic subsets infarct size and medical therapy*

The great variety of hemodynamic subsets noted in patients with acute myocardial in-

farction (8, 17) provides one rational basis for the selection of a specific form of treatment. The aim of therapy today should not only be hemodynamic support, but also the protection of the jeopardized ischaemic segments, which are often large. Treatment of hypovolemic hypotension by fluid challenge, or hyperdynamic cardiac action by beta blockade are examples of such physiological principles of therapy. However, the same therapeutic intervention may sometimes produce the opposite effect on the infarct size, depending on the prevailing physiological circumstances. For example, reports on vasodilators and infarct size (10) and on inotropic drugs and infarct size (33, 34) are controversial. Information on the immediate effect of therapeutic intervention should be available quickly and easily in order to permit appropriate modification of the treatment instituted.

#### *Methods for evaluating infarct size*

Methods for a convenient quantitative assessment of the final infarct size in man are so far lacking. The methods applied have mainly been creatine phosphokinase enzyme release, electrocardiographic ST segment and QRS mapping, and myocardial imaging by radioisotopes (22) (Table I). The echocardiographic scanning technique developed recently by us also seems to provide a suitable method of describing the site and size of asynergic wall motions in infarction (18, 51). However, in the acute stage of evolution of the infarction, the proper application of pharmacological intervention should be controlled very rapidly; it is useless to be told after several hours have elapsed that unsuitable treatment was going on, while waiting for the results! Of the methods in common use, only the electrocardiographic ST segment shifts are rapid enough to provide a means of immediately recognizing the directional course of the ischaemic process (Table I).

Evaluating ischaemic dysfunction, on the other hand, can be done directionally very quickly using electrophysiologic and metabolic methods, and by studying the regional

traction in a few seconds (26-68-69). This relationship has been repeatedly documented experimentally by segmental length and wall thickness measurements (4-28-64-65-68-74) (Fig. 1). Mechanical alteration even precedes the appearance of the ischemic ST segment shifts, and precedes even more the onset of measurable biochemical alterations (46, 27). The functional alteration of myocardial contractility is thus obviously one of the most sensitive markers of ischemia. Recovery after short ischemia may be noted more rapidly in mechanical function than in the ST segments, while after longer ischemia mechanical dysfunction persists despite normalization of the ST segments (4-64-69-72). Thus dissociation of these two sensitive markers of acute ischemia, mechanical and electrophysiological, is sometimes possible, depending on the nature and time course of the ischemic injury.

Experimentally abnormalities of the myocardial segmental wall motions are directly and very accurately visualized by ultrasound (28, 69). Recently local contraction abnormalities have also been described by echocardiography constantly in patients with myocardial infarction (11-18). However detection of the regional contraction kinetics in the entire human left ventricle naturally requires multiple beam directions. We have developed a multibeam single-beam echocardiographic technique called echoventrulography that is suitable for reaching almost every segment of the left ventricle (18, 51). Performance of the noninjected myocardium, the center of the infarcted area and the twilight zone between can be displayed using noninvasively and usually this technique in all patients. The method described in the following, together with apical ST segment shifts and hemodynamic measurements, was therefore used for comprehensive study of instantaneous directional effects of pharmacological intervention on the function of ischemic myocardial segments and hemodynamics in man. Beta stimulation and beta blockade were selected essential types of intervention with physiologically opposite cardiac effects.

### *A technical description of echoventrulography for the detection of regional wall motion abnormalities of the left ventricle in man*

The echoventrulography technique is based on the single-beam studies used sequentially from multiple directions to assess the segmental myocardial function of practically the entire left ventricle. Regional function can thus be studied from the upper and lower halves of the septal anterior lateral and posteroinferior left ventricular segments (18, 51).

The anatomical orientation is performed in a standard way and using four principal echo beam directions (Fig. 2) (51). Orientation is begun by finding the point on the chest wall from which the motion of both the anterior and posterior mitral leaflets is seen simultaneously. This point is usually situated in the 4th intercostal space about 1-2 cm left of the margin of the sternum, but there may be individual variations. The beam then meets the easily recognizable aortic root when the probe is moved upwards along the sternum. The anterior junction of the right ventricle and the septum is found by moving the probe from the left sternal border in a lateral direction and thereby tracing the narrowing of the right ventricular cavity towards the left ventricular anterior wall. The apex is recognized by the opposite motion of the anterior and inferolateral left ventricular walls downwards from the mitral point. The apical region of the left ventricle has also been reported by others to become well visualized by the low sites of the probe (11). The characteristic echoes of the anterior and posterior papillary muscles and the anterior and posterior edges of the mitral valve are other useful landmarks during orientation: the anterior posterior septal and lateral horizontal sections of the left ventricular circumference.

When the probe is moved from the mitral recording point to the left sternal margin, without changing its horizontal plane, and directed slightly inferiorly the conventional position (position 1 Fig. 2) for the left ven-



precordial ST mapping systems are applicable only to anterior and anterolateral infarctions. The convenient 12 lead electrocardiogram allows study of the inferoposterior infarctions, too, in the same way as in the vector ST segment approach (1). The 12 lead electrocardiogram has been shown recently to give a good picture of the ST segment shifts recorded by the extensive mappings, and it also predicts the final extent of infarct necrosis in man (3-15).

The sites of the precordial leads were modified somewhat to allow for the simultaneous precordial echocardiographic examination. The leads were permanently fixed and the recordings were always made with the patient in the same position. ST segment

shifts were measured 60 msec after the termination of the QRS deflection and using the PR segment as the isoelectric line. If the ST segment was markedly depressed it was included in the sum of the ST segment elevation too since the ST segment depression occurring in these patients reflects either the subendocardial injury current or a reciprocal shift to the main ST segment elevation (see Fig. 8).

#### *Relationship between ischaemia and the mechanical performance of myocardium*

Ischaemia of the myocardium is very closely related to the mechanical myocardial dysfunction. The ischaemic region loses its con-

## WHY SEGMENTAL WALL MOTION DETECTS ISCHEMIA?

MYOCARDIAL CONTRACTION IS GREATLY REDUCED, OR LOST, IN ISCHEMIA



NORMAL WALL MOTION



ISCHEMIA

10 SEC



ISCHEMIA

30 SEC

ECHO EQUALS ANGIO IN SENSITIVITY FOR DETECTION OF REGIONAL ASYNERGY

Fig. 1 The sequence of normal anterior wall segment motion changing into akinesic and paradoxical motion in increasing ischaemia is illustrated by echo in man.

The time course is taken from the experimental coronary artery ligation (ref. 68).

tricular transverse diameter is obtained. Left ventricular volumes and ejection fraction are usually calculated from these diameters using the cube function (14-51). The four standard precordial positions and axis directions are used for detailed assessment of the segmental wall motion (Fig. 2). At each precordial position the probe is directed as perpendicularly as possible towards the region desired. This is ascertained by rotating the probe with small steps and finding a direction so that the echo lines at the 2:1 scale from the myocardial layers move in a parallel way in both the A-mode and M-mode display (51-54).

The upper septal and posterolateral regions of the left ventricle are reached from position 1 (Fig. 2). Position 2 is about 2 cm lateral from the mitral valve point, i.e. positions 1 and 2 are about 5 cm apart. Thus beam axis traverses the upper posterior and free anterior wall regions (Fig. 2). Position 3 of the probe lies one intercostal space below position 1; this axis scans the inferolateral and septal regions in the lower half of the left ventricle. The lower free anterior and inferoposterior wall regions are recorded from position 4 one intercostal space below position 2 (Fig. 2). These standardized scanning sites are necessary in order to obtain reproducible data in the sequential studies.

Additional positions are used for more detailed estimation of the anterior wall asymmetry. High anterior (AW5), septal-apical (AW6) and mid-interseptal (AW7) regions are scanned between the four standard sites at the anterior side of the left ventricle (Fig. 2). Often even more lateral areas may be studied in cases where the left ventricle has enlarged laterally (AW8-14) (Fig. 2). The posterior wall segments are usually studied first. The same gain and reject levels are used for each segment. The fine adjustments are made by rotating the probe by slight movements according to the A-mode control. The regional M-mode scanning which has repeatedly shown optimal endocardial and epicardial echolines is photographed with a Polaroid camera from the memory scope screen. The anterior wall re-

gions are recorded in a similar way but a lower decibel gain is usually utilized.

The regional myocardial function is analyzed quantitatively by measuring the amplitude of the systolic wall motions and the systolic thickening at each site. The velocity of systolic segment motions has not contributed anything to these measurements (49). The mean normal left ventricular anterior wall motion amplitude is  $4.9-5.7 \pm 1.4$  (s.d.) mm (AW1-4) and the mean normal posterior wall motion amplitude is  $7.9-8.5 \pm 1.8$  (s.d.) mm (PW1-4) (49). The difference is probably caused by the recoil motion of the whole heart 1-2 mm anteriorly in systole (51).

The "total" regional function of the left ventricle is studied by summing up the individual regional wall motion amplitudes. The echocardiographic contraction index (50) is obtained in this way from the sum of the amplitude at the 8 standard sites (PW1-4 and AW1-4 Fig. 2). The sum is normalized by dividing it by the sum of the corresponding mean normal amplitudes (49-50). In left ventricle contracting asymmetrically this composite segmental function describes the teamwork of the normal, often hypercontractile, myocardium together with the asynergic segments (53).

While the echocardiography technique markedly expands the capacity of the single beam echo to study the left ventricular performance in detail, it also poses many technical problems (51). Elderly emphysematous patients and obese subjects require considerably time and effort before acceptable recordings are obtained. Correct orientation to the particular segment in the repeated studies requires careful marking of the precordial sites used for the study thereafter; it is easier to select the correct beam direction using the perpendicular echo line motion patterns.

#### *Reliability / echocardiography in detecting the size and size / abnormal wall motion*

The high accuracy of the multidirectional echocardiography method in detecting

# WALL MOTIONS IN 2:1 SCALE



NORMAL



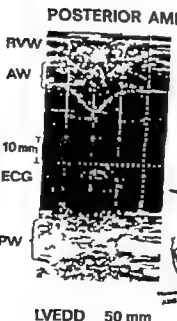
PARADOXICAL



HYPOKINETIC



HYPERKINETIC



POSTERIOR AMI

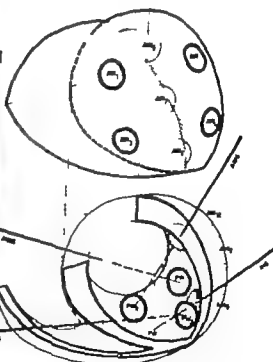


Fig. 2 The echocardiography technique is based on multi-axis echobeam recording from various precordial sites. The four basic precordial transducer sites in the 4th and 5th intercostal spaces are illustrated with respective schematic segments being scanned in the left ventricle. The other precordial numbers refer to

the additional sites used for study of the anterior wall. Characteristic segment motion patterns seen in myocardial infarction in the 2:1 scale are also displayed. The transverse axis of the left ventricle displays a paradoxical motion of the posterior wall.

Table 11 Summary of Differences in the E-Recording Wave Dimensions Recorded in Patients with Acute Myocardial Infarction

Time interval (min)	L.V. diastolic diameter	Healthy zone		Wall thickness		Infarct zone Amplitude	Border zone Amplitude	Infarct + border zone		
		Amplitude	diastolic	diastolic	systolic			Wall thickness	systolic	
		0-10	0-60	0-10	0-60	0-10	0-60	0-10	0-60	
S.E. (mm)	0.56	0.34	0.20	0.26	0.63	0.44	0.20	0.24	0.27	
S.D. (mm)	1.37	0.90	0.49	0.63	1.53	1.07	0.45	0.65	0.89	
N	6	7	6	6	6	5	7	6	7	

with chronic coronary artery obstruction verified by selective coronary arteriography. The wall motion of the ventricular segment known to be perfused by a markedly stenosed artery was measured 3 minutes after an increase in the heart rate with atrial pacing. Without a single exception the wall motion amplitude decreased during the pacing, and finally it often became paradoxical, in parallel with, but preceding, the appearance of the electrocardiographic ischaemic ST segment depression (Fig. 3). The left ventricular size also increased acutely instead of the normal reduction seen during pacing. Both the ischaemic myocardial segment motions and the ST segments normalized again within 2-3 minutes after the pacing was stopped. Besides confirming the sensitive physiological relationship between ischaemia and myocardial segmental function, this study also demonstrates the ability of the echocardiography technique to document such changes rapidly.

#### Hemodynamic measurements

A Swan-Ganz thermodilution catheter No. 7 was inserted into the pulmonary artery branch and checked fluoroscopically. Cardiac output was determined as an average of 3 to 4 ice-cold saline injections measured with an Edwards 9510 thermodilution computer.

The pressure transducer zero was positioned at the mid-thoracic level. Arterial pressure was measured with a cuff sphygmomanometer with 2 mmHg reading interval. The following hemodynamic variables were recorded: heart rate, systolic and diastolic arterial pressures, pulmonary capillary wedge pressure, stroke volume, cardiac output, left ventricular stroke work and rate pressure product. The mean arterial pressure was approximated for the calculations by the sum of the diastolic pressure and one third of the pulse pressure.

#### Patients and study protocol

Forty-two patients, 36 men and 6 women, ranging in age from 34 to 78 mean 55.2 years, were studied during the acute phase of what was usually their first myocardial

regional ventricular asynergy has been proved by correlative studies with electrocardiogram, cineventriculography and autopsy findings in patients with myocardial infarction. In acute myocardial infarction the presence of abnormal regional motion was confirmed in all subjects in a series of 30 consecutive patients (18) thereafter the same held true in about one hundred other patients. The septal anterior posteroinferior or lateral site of acute transmural myocardial infarction by serial electrocardiograms was in complete agreement with the location of the asynergic motion noted in echoventriculography.

In 42 patients studied for coronary artery bypass surgery the left ventricular cineangiography was related to the echoventriculography (50). The presence of an asynergic segment in angiography was always correctly predicted by echoventriculography as was the quantitative degree of the abnormal motion. Angiographically normal segments were similarly normal in echoventriculography (50).

So far 20 patients with fatal myocardial infarction were studied with echo shortly before death. The borders of the infarct were assessed by echo to fall into 7 equal sectors, each at the upper and the lower halves of the left ventricle. At autopsy a variation over the sector determined echocardiographically was exceptional and only occurred at the furthest lateral wall and the posteroseptal areas, which are comparatively blind to the single beam (unpublished). Usually the borders of the infarct as shown by echo and a pathologic anatomic examination agreed within 1–2 cm.

#### *Reproducibility of echo measurements*

The reproducibility of the present technique in normal left ventricle was tested in a series of healthy subjects (49). In 34 paired measurements the differences in the systolic wall motion amplitudes recorded 10 minutes apart remained insignificant the standard error of differences was 0.1 mm and the standard deviation of differences 0.7 mm. For the wall thickness in diastole these figu-

res were 0.2 mm and 1.2 mm, respectively in systole 0.4 and 1.2 mm. Left ventricular end-diastolic diameters were studied in 39 paired comparisons. The standard error of differences was 0.3 mm and the standard deviation of differences 1.7 mm (NS). One month later the standard error of differences of all these variables in 53 paired studies also remained insignificant, the standard error of differences for the systolic wall motion amplitudes was 0.15 mm.

This reproducibility of the sequential measurements is highly dependent on the strict standardization of the probe directions relative to the anatomical reference sites described above. For the segmental wall motion the perpendicular beam direction must always be controlled by the parallel echo line motions from the different myocardial layers of the segment being examined.

In acute myocardial infarction the echoventriculographic data were repeatedly studied in 7 patients in order to test the short term stability of abnormal segment function during the first day of infarction thereafter only slight changes are usually seen (52). The measurements were repeated first 5 to 10 minutes and then one hour after the initial examination. Here the precordial sites for the border zone segments were marked on the chest wall in the same manner as in the later intervention studies, to ascertain an identical orientation in the repeat studies. No significant variations were noted (Table II). The standard error of differences in the wall motion amplitudes and thicknesses at the healthy infarcted and border zone segments were each 0.2 mm and of the end-diastolic left ventricular diameter 0.7 mm. These reproducibility studies then confirm the value of studying the segmental function changes quantitatively in ischaemic hearts, too, as a framework for the intervention studies.

#### *Pacing-induced myocardial ischaemia*

We also demonstrated the sensitivity of myocardial mechanics as a marker of acute ischaemia by an atrial pacing of 5 patients

Table 11 Statistics of Differences in the Echocardiographic Parameters Recorded in Patients with Acute Myocardial Infarction

Time interval (min)	L.V. diastolic diameter	Healthy zone		Infarct zone		Border zone		Infarct + border zones		Wall thickness	
		Amplitude		Amplitude		Amplitude		W/I thickness			
										diastolic	systolic
		0-10	0-60	0-10	0-60	0-10	0-60	0-10	0-60	0-10	0-60
S.E. (mm)	0.56	0.24	0.20	0.20	0.44	0.20	0.26	0.20	0.24	0.27	0.21
S.D. (mm)	1.37	0.90	0.49	0.45	1.07	0.49	0.70	0.65	0.65	0.89	0.78
N	6	6	6	6	6	6	7	6	7	11	14

with chronic coronary artery obstruction verified by selective coronary arteriography. The wall motion of the ventricular segment known to be perfused by a markedly stenosed artery was measured 3 minutes after an increase in the heart rate with atrial pacing. Without a single exception the wall motion amplitude decreased during the pacing, and finally it often became paradoxical, in parallel with, but preceding, the appearance of the electrocardiographic ischaemic ST segment depression (Fig. 5). The left ventricular size also increased acutely instead of the normal reduction seen during pacing. Both the ischaemic myocardial segment motions and the ST segments normalised again within 2-3 minutes after the pacing was stopped. Besides confirming the sensitive physiological relationship between ischaemia and myocardial segmental function, this study also demonstrates the ability of the echocardiography technique to document such changes rapidly.

#### Hemodynamic measurements

A Swan-Ganz thermodilution catheter No. 7 was advanced into the pulmonary artery branch and checked fluoroscopically. Cardiac output was determined as an average of 3-4 ice-cold saline injections measured with an Edward 9510 thermodilution computer.

The pressure transducer zero was positioned at the mid-thoracic level. Arterial pressure was measured with cuff sphygmomanometer with a 2 mmHg reading interval. The following hemodynamic variables were recorded: heart rate, systolic and diastolic arterial pressures, pulmonary capillary wedge pressure, stroke volume, cardiac output, left ventricular stroke work and rate pressure product. The mean arterial pressure was approximated for the calculations by the sum of the diastolic pressure and one third of the pulse pressure.

#### Patients and study protocol

Forty-two patients, 36 men and 6 women, ranging in age from 34 to 78 (mean 55.2 years), were studied during the acute phase of what was usually their first myocardial

regional ventricular asynergy has been proved by correlative studies with electrocardiogram cineventriculography and autopsy findings in patients with myocardial infarction. In acute myocardial infarction the presence of abnormal regional motion was confirmed in all subjects in a series of 30 consecutive patients (18) thereafter the same held true in about one hundred other patients. The septal, anterior posteroinferior or lateral site of acute transmural myocardial infarction by serial electrocardiograms was in complete agreement with the location of the asynergic motion noted in echoventriculography.

In 42 patients studied for coronary artery bypass surgery the left ventricular cineangiography was related to the echoventriculography (50). The presence of an asynergic segment in angiography was always correctly predicted by echoventriculography as was the quantitative degree of the abnormal motion. Angiographically normal segments were similarly normal in echoventriculography (50).

So far 20 patients with fatal myocardial infarction were studied with echo shortly before death. The borders of the infarct were assessed by echo to fall into 7 equal sectors, each at the upper and the lower halves of the left ventricle. At autopsy a variation over the sector determined echocardiographically was exceptional and only occurred at the furthest lateral wall and the posteroseptal areas, which are comparatively blind to the single beam (unpublished). Usually the borders of the infarct as shown by echo and a pathologic anatomic examination agreed within 1–2 cm.

#### *Reproducibility of echo measurements*

The reproducibility of the present technique in normal left ventricle was tested in a series of healthy subjects (49). In 34 paired measurements the differences in the systolic wall motion amplitudes recorded 10 minutes apart remained insignificant, the standard error of differences was 0.1 mm and the standard deviation of differences 0.7 mm. For the wall thickness in diastole these fig-

ures were 0.2 mm and 1.2 mm, respectively, in systole 0.4 and 1.2 mm. Left ventricular end-diastolic diameters were studied in 39 paired comparisons. The standard error of differences was 0.3 mm and the standard deviation of differences 1.7 mm (NS). One month later the standard error of differences of all these variables in 53 paired studies also remained insignificant, the standard error of differences for the systolic wall motion amplitudes was 0.15 mm.

This reproducibility of the sequential measurements is highly dependent on the strict standardization of the probe directions relative to the anatomical reference sites described above. For the segmental wall motion the perpendicular beam direction must always be controlled by the parallel echo line motions from the different myocardial layers of the segment being examined.

In acute myocardial infarction the echoventriculographic data were repeatedly studied in 7 patients in order to test the short term stability of abnormal segment function during the first day of infarction thereafter only slight changes are usually seen (52). The measurements were repeated first 5 to 10 minutes and then one hour after the initial examination. Here the precordial sites for the border zone segments were marked on the chest wall in the same manner as in the later intervention studies, to ascertain an identical orientation in the repeat studies. No significant variations were noted (Table II). The standard error of differences in the wall motion amplitudes and thicknesses at the healthy infarcted and border zone segments were each 0.2 mm, and of the end diastolic left ventricular diameter 0.7 mm. These reproducibility studies then confirm the value of studying the segmental function changes quantitatively in ischaemic hearts, too, as a framework for the intervention studies.

#### *Pacing-induced myocardial ischaemia*

We also demonstrated the sensitivity of myocardial mechanics as a marker of acute ischaemia by an atrial pacing of 5 patients

segment elevations analyzed at 15 minute intervals in 20 patients were  $10.6 \pm 7.8$  and  $11.4 \pm 10.1$  mV (7.5 % difference). Heart rate variations analyzed in 13 patients were  $83.1 \pm 31.3$  and  $82.1 \pm 31.5$  (3.6 % difference) pulmonary capillary wedge pressures were  $11.2 \pm 4.4$  and  $11.9 \pm 4.6$  mmHg (6.3 % difference) and stroke volumes  $71.7 \pm 29.7$  and  $73.7 \pm 28.6$  (2.8 % difference). The echocardiographic variables for short-term stability without any intervention were reported earlier (Table II). The wall motion amplitude variations remained within 1 mm, as is the case in normal subjects (49).

**Dopamine** (Dopamin® Orion, Finland) infusion in 20 patients was first administered at rate of 250  $\mu$ g per minute. After 5 minutes all the measurements were repeated. The time was kept short since catecholamines may rapidly increase myocardial ischemia. If no deleterious effects were noted (chest pain, arrhythmias, marked elevation of ST segments, or increase in the heart rate by more than 30 beats per minute) the dopamine drip speed was increased to 500  $\mu$ g/min (14 patients) in some cases thereafter to 750  $\mu$ g/min. After these recordings were completed the infusion was stopped for half an hour.

**Practolol** The second control recording after 30 minutes of recovery was followed by an intra-arterial injection of 5 mg practolol (Laidin I.C.I., England). The drug was injected over a period of 2–3 minutes; the same patients treated first with dopamine. The recordings were made 15 minutes later. The effect of practolol was compared with the second batch of control data, recorded half an hour after dopamine was stopped. Practolol was not given to 1 of these patients due to cardiogenic shock.

**Pindolol** After the control recordings, 0.2 mg pindolol (Vinkem Sandoz, Switzerland) was injected in 22 other patients, who were not studied using dopamine and practolol. The drug response was again studied 15 minutes later. All the statistical analyses were performed using the t-test for paired data.

## Results

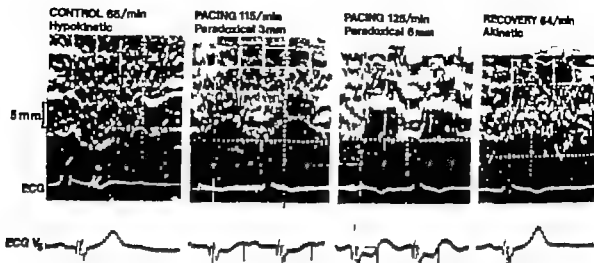
### Dopamine

Hemodynamic performance increased significantly in all 20 patients with dopamine in a dose-dependent way (Table III). The average cardiac output increased by 21.6 % with the 250  $\mu$ g/min dose and by 38.1 % with the 500–750  $\mu$ g/min dose ( $p < 0.001$ ). The increase was due more to the stroke volume becoming augmented (14.9 and 28.5 %  $p < 0.001$ ) than to the faster heart rate which increased by 7.5 % and 19.9 % with these respective dosages ( $p < 0.001$ ). The arterial pressure tended to rise with the larger dose only and so did the stroke work (13.1 to 21.1 %,  $p < 0.001$ ). The rate pressure product, reflecting the myocardial oxygen consumption (29) increased with increasing dose (5.6 to 13.4 %  $p < 0.001$ ). Pulmonary capillary wedge pressure decreased insignificantly by an average of 2 mmHg. Only one did dopamine induce frequent ventricular ectopic beats requiring that infusion be stopped; in this patient the rate pressure product increased by one third.

**Left ventricular regional performance** Dopamine enhanced the motion amplitude of the healthy myocardium by 12.4 % (from  $9.7 \pm 2.8$  to  $10.9 \pm 3.9$  mm,  $p < 0.025$ ) but by no more with the larger dose (Table IV). The left ventricular end-diastolic diameter was markedly reduced from  $51.7 \pm 6.2$  to  $48.0 \pm 6.5$  mm ( $p < 0.0005$ ). This 7.2 % decrease in diameter meant a 20.0 % smaller end-diastolic volume by the cube function. However no improvement occurred in the ischemic myocardial segments (Table IV, Fig. 4 and 5). The mean change after both doses of dopamine was only 0.1 mm. In 10 patients the combined segment function improved and in others it deteriorated. Similarly only a negligible increase (7.4 %, NS) was noted in the local regional performance by the echocardiographic contraction index, being the result of the enhanced motion of healthy myocardium and the ischemic segments showing variable responses only.



## ISCHEMIC MYOCARDIAL DYSFUNCTION INDUCED WITH ATRIAL PACING



*Fig 3 Myocardial ischaemia is induced with atrial pacing in a patient with coronary artery obstruction. The initially hypokinetic anterior wall motion is changed drastically paradoxical*

*ST segment depression and anginal pain appeared simultaneously. After stopping the pacing all changes were reversed.*

myocardial infarction. Five patients had a reinfarction, and 7 a nontransmural infarction. The acute myocardial infarction was confirmed by chest pain, electrocardiographic serial changes and myocardial enzyme elevations. Twenty-six patients had anterior and 16 posteroinferior infarction. Fourteen patients had uncomplicated infarction, 22 had clinically moderate heart failure and 6 had severe low output state, cardiogenic shock or frank pulmonary edema (8). All patients were studied during the first 48 hours from the onset of pain, the average time being 17.8 hours. About one half of the patients were studied between 12 and 24 hours after the onset of symptoms, 15 within 12 hours, and 5 after more than 24 hours. Informed consent for the procedure was obtained.

Twenty patients were studied using dopamine. Of these 20 patients, 6 had uncomplicated infarction, 8 moderate heart failure and 6 severe left ventricular failure. Specifically, we wanted to study any contrasting effects on signs of ischaemia induced sequentially by both beta stimulation (dopamine)

and beta blockade (practolol) in the same patients. Nineteen patients were studied sequentially using dopamine infusions followed by practolol injection. Twenty-two other patients received no inotropic stimulation, and the effect of beta blockade was studied using another beta blocking drug, pindolol.

A period of 20–30 minutes was allowed for stabilization after application of the hemodynamic, electrocardiographic and echocardiographic recording systems. The patients served as their own controls due to the short duration of the study. In this way even the minor effects of intervention are better defined despite the highly varied nature of acute infarction in individual patients. Eleven patients received lidocaine 1–2 mg/minute during the study. Oxygen administration was kept unchanged throughout the study since this can influence the ST segments (36).

Control measurements were made repeatedly in each patient for hemodynamics and ST segments at 15 minute intervals to achieve a stable control state. The variation in the repeated measurements remained non-significant and virtually negligible. The ST

# MYOCARDIAL MECHANICAL AND ST SEGMENT RESPONSES TO DOPAMINE AND BETA BLOCKING DRUGS

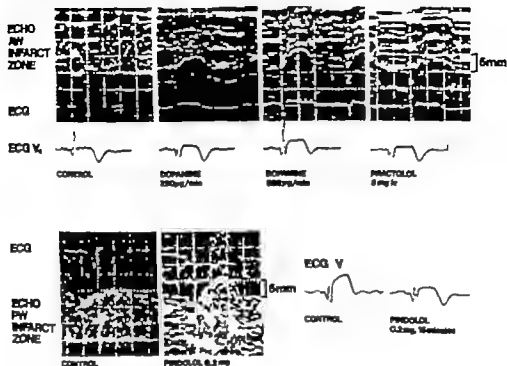


Fig 4 Illustrative wall motion changes of the ischaemic segment by echo. Deterioration of the contractile function is progressive after increasing doses of dopamine. Pindolol thereafter diminished the paradoxical motion.

A marked recovery of mechanical function is noted in another patient after pindolol. The ST segment changes are parallel.

ST segments increased in size with the small dose of dopamine (10.5 %, NS) but deteriorated markedly with the larger dose (42.4 %,  $p < 0.0025$  Table IV Fig 6).

**Dopamine and the hemodynamic indices of infarction.** The acute effect of dopamine on the markers of ischaemia was influenced by the initial hemodynamic state of the patient. In 14 of the 20 patients who had uncomplicated infarction or moderate heart failure, dopamine also made the ST segment deviations and the asymmetric motion worse (Table V). In contrast, slight reduction of the ST segment by a mean of  $-12.5$  % (range  $-3$  to  $-25$  %) by the dopamine was

noted in 5 of the 6 patients with severe left ventricular failure or shock after infarction. In 2 of these this continued with the high dose as well (Fig. 7). The pulmonary capillary wedge pressure decreased at the same time in 2 of the latter patients by more than 5 mmHg, and improved mechanical function was also noted in their ischaemic segments.

## Beta blockade by pindolol and practolol

**Hemodynamic performance** did not deteriorate in the 22 patients treated with a 0.2 mg dose of pindolol. These patients had an uncomplicated infarction or moderate left heart failure. The most significant change was the

Table III Hemodynamic Effects of Dopamine Infusion in Patients with Acute Myocardial Infarction (Mean  $\pm$  SD)

	Control	Dopamine 250 $\mu$ g/min N = 20	Control	Dopamine 500-750 $\mu$ g/min N = 14	P
Heart rate (bpm)	83.7 $\pm$ 21.7	90.0 $\pm$ 23.4	86.8 $\pm$ 19.5	96.3 $\pm$ 21.1	< 0.001
Systolic blood pressure (mm Hg)	127.6 $\pm$ 17.5	126.0 $\pm$ 18.1	129.5 $\pm$ 14.6	132.9 $\pm$ 19.5	NS
Pulmonary capillary wedge pressure (mm Hg)	12.7 $\pm$ 5.1	12.0 $\pm$ 5.0	11.9 $\pm$ 5.5	10.8 $\pm$ 4.6	NS
Cardiac output (l/min)	6.0 $\pm$ 1.6	7.3 $\pm$ 1.7	6.3 $\pm$ 1.7	8.7 $\pm$ 2.4	< 0.001
Stroke volume (ml)	75.4 $\pm$ 25.8	86.6 $\pm$ 29.2	76.9 $\pm$ 29.2	98.8 $\pm$ 37.2	< 0.001
Stroke work (g m)	85.7 $\pm$ 27.6	96.9 $\pm$ 32.6	86.6 $\pm$ 30.0	104.9 $\pm$ 37.1	< 0.001
Rate pressure product (mm Hg bpm)	10634 $\pm$ 3286	11232 $\pm$ 3532	10988 $\pm$ 2900	12438 $\pm$ 3102	< 0.01

Table IV Myocardial Regional Function and ST Segment after Dopamine Infusion in Patients with Acute Myocardial Infarction (Mean  $\pm$  SD)

	Control	Dopamine 250 $\mu$ g/min N = 20	Control	Dopamine 500-750 $\mu$ g/min N = 14	P
LV diastolic diameter (mm)	51.7 $\pm$ 6.2	48.4 $\pm$ 6.9	52.8 $\pm$ 6.1	49.0 $\pm$ 6.3	< 0.0005
Infarct zone amplitude (mm)	-1.7 $\pm$ 1.4	-1.9 $\pm$ 1.7	-1.8 $\pm$ 1.4	-1.8 $\pm$ 2.3	NS
Border zone amplitude (mm)	2.7 $\pm$ 2.3	2.9 $\pm$ 3.4	3.2 $\pm$ 1.7	4.0 $\pm$ 4.4	NS
Combined ischaemic zones amplitude (mm)	0.4 $\pm$ 2.9	0.5 $\pm$ 3.6	0.9 $\pm$ 1.6	0.8 $\pm$ 4.4	NS
Healthy zone amplitude (mm)	9.7 $\pm$ 2.8	10.9 $\pm$ 3.9	9.4 $\pm$ 3.3	10.6 $\pm$ 3.7	NS
Echocardiographic contraction index (%)	58.3 $\pm$ 20.1	62.7 $\pm$ 19.7	62.3 $\pm$ 23.6	66.1 $\pm$ 18.7	NS
ST segment (%)	100	+10.5 $\pm$ 29.2	100	+42.4 $\pm$ 49.6	< 0.0025

# HEMODYNAMIC SUBSET INOTROPIC STATE AND ST SEGMENT SHIFTS

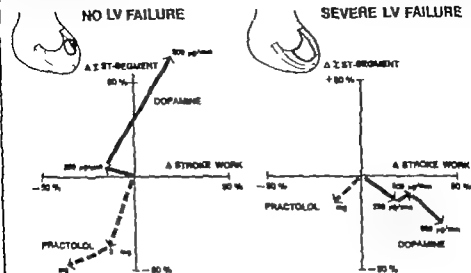


Fig 7 1 patient with uncomplicated acute myocardial infarction dopamine consistently increased ischemic ST segment elevation while in severe pump failure marked hemodynamic improvement was seen achieved without any

electrocardiographic increase in ischemia. A small dose of beta blocking drug unexpectedly effectively reduced signs of myocardial ischemia it was soon tolerable even in marked heart failure

Table VI Hemodynamic Effects of Pindolol in Patients with Acute Myocardial Infarction (Mean  $\pm$  SD).

	Control	Pindolol 0.2 mg iv	P
	N = 22		
Heart rate (bpm)	73.4 $\pm$ 12.4	68.6 $\pm$ 9.7	< 0.001
Systolic blood pressure (mm Hg)	135.9 $\pm$ 23.6	128.8 $\pm$ 24.3	< 0.005
Pulmonary capillary wedge pressure (mm Hg)	13.2 $\pm$ 4.4	13.1 $\pm$ 4.1	NS
Cardiac output (l/min)	5.6 $\pm$ 1.0	4.8 $\pm$ 1.3	< 0.01
Stroke volume (ml)	77.3 $\pm$ 17.6	72.1 $\pm$ 21.7	NS
Stroke work (g m)	94.8 $\pm$ 30.0	85.7 $\pm$ 32.7	< 0.05
Rate pressure product (mm Hg bpm)	10158 $\pm$ 2571	8831 $\pm$ 2089	< 0.0005

# WALL MOTION IN THE ISCHEMIC MYOCARDIAL SEGMENTS AFTER DOPAMINE AND BETA BLOCKING DRUGS

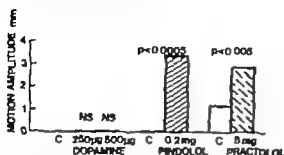


Fig 5 The mean change from control (C) in the systolic wall motion amplitudes of the ischaemic myocardial segments by echo remained zero after dopamine. In contrast a remarkable recovery of the mechanical function was observed after small doses of beta blocking drugs

slowing of the heart rate by an average of 7 beats per minute ( $-9.0\%$   $p<0.001$  Table VI). Cardiac output decreased by  $14.3\%$  ( $p<0.01$ ) due to the constant reduction of the heart rate while the stroke volume remained virtually unchanged ( $-6.7\%$  NS). The left ventricular filling pressure remained very stable i.e.  $13.2\pm 4.4$  mmHg before, and  $13.2\pm 4.1$  mmHg after pindolol. Left ventricular stroke work ( $-9.6\%$ ) systolic arterial pressure ( $-5.2\%$ ) and the rate pressure product ( $-13.8\%$ ) all decreased significantly (Table VI). In one patient only pindolol caused a fall of arterial pressure by more than 20 mmHg.

A rather exceptional demonstration of an obvious recovery of the ischaemic segments was the reduction of marked ischaemic papillary muscle dysfunction in 2 patients immediately after injection of pindolol (Fig 8).

# ST SEGMENT SHIFTS AFTER DOPAMINE AND BETA BLOCKING DRUGS

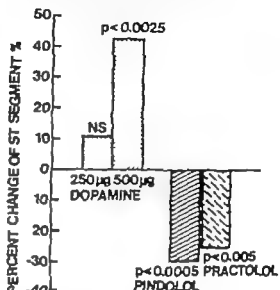


Fig 6 The sensitivity of the mean ST segment shift response to drugs increasing or decreasing cardiac work is displayed. Pindolol was given subsequently to the same patients who were first studied by dopamine.

Left ventricular regional performance of the ischaemic heart was markedly modified by the small-dose beta blockade. The systolic motion both at the center of infarction and at the ischaemic border zone increased markedly by 0.2 mg of pindolol alone and somewhat less with 5 mg of pindolol given subsequent to dopamine. With pindolol the improvement of the motions of both ischaemic segments analyzed together (infarct center + border zone) was from  $0.1\pm 3.5$  to  $3.4\pm 3.8$  mm ( $p<0.0005$  table VII Fig 3). Related to the respective normal anterior and

Table V Hemodynamic Subset, Dopamine and ST Segment Shift

Subset	ST $\Psi$	ST $\Psi > A$	ST $A$	Total
Uncomplicated or moderate left ventricular failure	0	6	8	14
Severe pump failure	5	0	1	6

$p<0.001$

**Table VII Myocardial Regional Function and ST Segments after Pindolol in Patients with Acute Myocardial Infarction (Mean  $\pm$  SD)**

	Control	Pindolol 0.2 mg iv	P
	N = 22		
LV diastolic diameter (mm)	49.4 $\pm$ 6.2	49.5 $\pm$ 3.9	NS
Infarct zone amplitude (mm)	-1.1 $\pm$ 1.8	0.3 $\pm$ 1.9	< 0.0005
Border zone amplitude (mm)	1.2 $\pm$ 2.6	3.5 $\pm$ 2.5	< 0.0005
Combined ischaemic zones amplitude (mm)	0.1 $\pm$ 3.5	3.4 $\pm$ 3.6	< 0.0025
Healthy zone amplitude (mm)	9.3 $\pm$ 2.4	9.2 $\pm$ 2.6	NS
Echocardiographic contraction index (%)	64.1 $\pm$ 17.1	75.6 $\pm$ 19.7	< 0.0005
ST segment (%)	100	-30.0 $\pm$ 20.9	< 0.0005

needed to contract in a similar way before and after beta blockade the average amplitude decreased by only 0.1 mm with pindolol and 0.2 mm with practolol. Thus the "total" regional function assessed by an echocardiographic contraction index improved by about 20 %, due to recovery of motion in the ischaemic segments. Neither did beta blockade cause any dilation of the left ventricular cavity size (Table VII and VIII).

ST segments improved by 30.0 % after

pindolol ( $p < 0.0005$ ) and by 25.3 % after practolol ( $p < 0.005$ ) (Tables VII and VIII, Fig. 6). A minor deterioration (<10 %) of ST segments occurred in 1 of the 22 patients with pindolol and in 1 of the 19 patients with practolol.

Chest pain present in 13 patients during injection of the beta blocking drugs disappeared within 1-3 minutes in 11 these patients.

**Table VIII Myocardial Regional Function and ST Segments after Practolol in Patients with Acute Myocardial Infarction (Mean  $\pm$  SD).**

	Control	Practolol 5 mg i	P
	N = 19		
LV diastolic diameter (mm)	52.8 $\pm$ 6.3	51.8 $\pm$ 6.9	NS
Infarct zone amplitude (mm)	-1.6 $\pm$ 1.7	-0.5 $\pm$ 2.4	< 0.005
Border zone amplitude (mm)	2.9 $\pm$ 2.2	3.9 $\pm$ 2.3	< 0.025
Combined ischaemic zones amplitude (mm)	1.3 $\pm$ 2.4	2.9 $\pm$ 3.0	< 0.005
Healthy zone amplitude (mm)	9.2 $\pm$ 3.0	9.0 $\pm$ 2.5	NS
Echocardiographic contraction index (%)	55.0 $\pm$ 19.8	66.4 $\pm$ 27.3	< 0.025
ST segment (%)	100	-25.3 $\pm$ 30.3	< 0.005

posterior segment amplitudes (49) the fractional improvement is then 25.6 % after pindolol. This change occurred without exception. The greatest improvement was a 9 mm increase in the motion of the ischaemic segments. In 4 nontransmural infarctions, the mean improvement with pindolol by 5.5 mm exceeds the average value.

With practolol, the recovery at the ischaemic segments was from the control value of

$1.2 \pm 2.4$  to  $2.9 \pm 3.0$  mm after the drug, i.e. fractionally 13.1 % of the normal amplitudes ( $p < 0.005$  Table VIII Fig 5). The best improvement with practolol was a 7 mm increase in the ischaemic segments. A slight deterioration of less than 1 mm occurred in the ischaemic segments in 3 of the 17 patients (17.5 %) with practolol, and never with pindolol.

Uninvolved myocardial segments con-

## ISCHEMIC PAPILLARY MUSCLE DYSFUNCTION

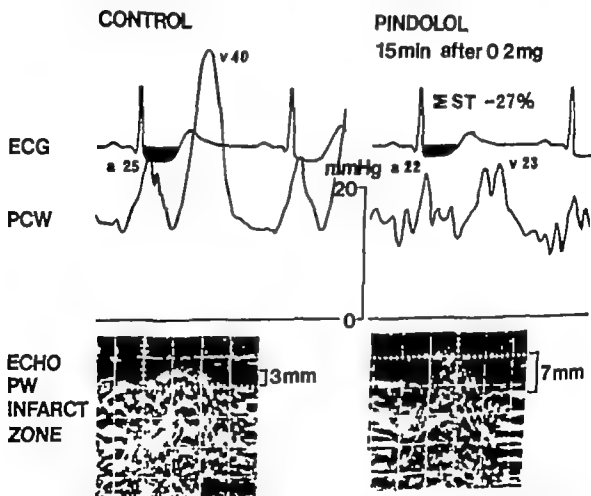


Fig 8 Marked ischaemic papillary muscle dysfunction in a patient with acute myocardial infarction produced peak of 40 mmHg in the pulmonary capillary wedge pressure (PCW). After 0.2 mg pindolol intravenously the wave form of the wedge pressure is almost normalised. Simultaneously ST segment depression (lead

V6) indicating subendocardial ischaemic injury is reduced and the myocardial wall motion of the posterolateral segment improved by echo from 3 mm to 7 mm. The recovery of function in ischaemic myocardial segments explain the relief of the functional subvalvular mitral incompetence.

**Table VII Myocardial Regional Function and ST Segments after Pindolol in Patients with Acute Myocardial Infarction (Mean  $\pm$  SD)**

	Control	Pindolol 0.2 mg iv N = 22	P
LV diastolic diameter (mm)	49.4 $\pm$ 6.2	49.5 $\pm$ 5.9	NS
Infarct zone amplitude (mm)	-1.1 $\pm$ 1.8	0.3 $\pm$ 1.9	< 0.0005
Border zone amplitude (mm)	1.2 $\pm$ 2.6	3.5 $\pm$ 2.5	< 0.0005
Combined ischaemic zones amplitude (mm)	0.1 $\pm$ 3.5	3.4 $\pm$ 3.6	< 0.0005
Healthy zone amplitude (mm)	9.3 $\pm$ 2.4	9.2 $\pm$ 2.6	NS
Echocardiographic contraction index (%)	64.1 $\pm$ 17.1	75.6 $\pm$ 19.7	< 0.0005
ST segment (%)	100	-30.0 $\pm$ 20.9	< 0.0005

need to contract in a similar way before and after beta blockade: the average amplitude decreased by only 0.1 mm with pindolol and 0.2 mm with practolol. Thus the regional function assessed by an echocardiographic contraction index improved by about 20 % due to recovery of motion in the ischaemic segments. Neither did beta blockade cause any dilation of the left ventricular cavity size (Table VII and VIII).

ST segments improved by 30.0 % after

pindolol ( $p < 0.0005$ ) and by 25.3 % after practolol ( $p < 0.005$ , Tables VII and VIII, Fig. 6). A minor deterioration (<10 %) of ST segments occurred in 1 of the 22 patients with pindolol and in 1 of the 19 patients with practolol.

Chest pain present in 13 patients during injection of the beta blocking drugs disappeared within 1-3 minutes in 11 of these patients.

**Table VIII Myocardial Regional Function and ST Segments after Practolol in Patients with Acute Myocardial Infarction (Mean  $\pm$  SD)**

	Control	Practolol 5 mg N = 19	P
LV diastolic diameter (mm)	52.8 $\pm$ 6.3	51.8 $\pm$ 6.5	NS
Infarct zone amplitude (mm)	-1.6 $\pm$ 1.7	-0.5 $\pm$ 2.4	< 0.005
Border zone amplitude (mm)	2.9 $\pm$ 2.2	3.9 $\pm$ 2.3	< 0.025
Combined ischaemic zones amplitude (mm)	1.2 $\pm$ 2.4	2.9 $\pm$ 3.0	< 0.005
Healthy zone amplitude (mm)	9.2 $\pm$ 3.0	9.0 $\pm$ 2.5	NS
Echocardiographic contraction index (%)	55.0 $\pm$ 19.8	66.4 $\pm$ 27.3	< 0.025
ST segment (%)	100	-25.3 $\pm$ 30.3	< 0.005



posterior segment amplitudes (49) the fractional improvement is then 25.6 % after pindolol. This change occurred without exception. The greatest improvement was a 9 mm increase in the motion of the ischaemic segments. In 4 nontransmural infarctions, the mean improvement with pindolol by 5.5 mm exceeds the average value.

With practolol the recovery at the ischaemic segments was from the control value of

$1.2 \pm 2.4$  to  $2.9 \pm 3.0$  mm after the drug, i.e. fractionally 13.1 % of the normal amplitudes ( $p < 0.005$  Table VIII Fig 5). The best improvement with practolol was a 7 mm increase in the ischaemic segments. A slight deterioration of less than 1 mm occurred in the ischaemic segments in 3 of the 17 patients (17.5 %) with practolol and never with pindolol.

Uninvolved myocardial segments conti

## ISCHEMIC PAPILLARY MUSCLE DYSFUNCTION

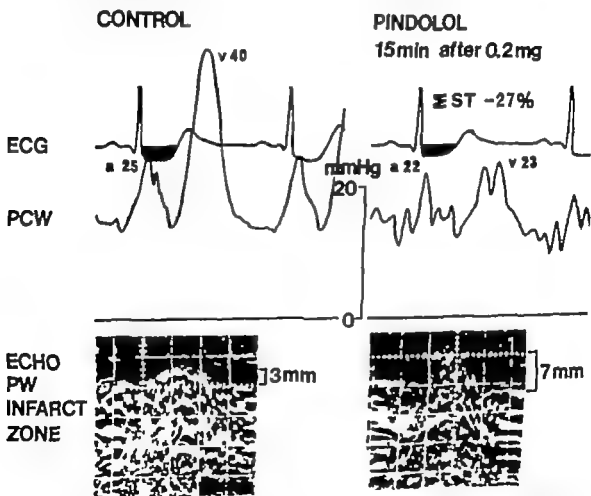


Fig 8 Marked ischaemic papillary muscle dysfunction in a patient with acute myocardial infarction produced peak of 40 mmHg in the pulmonary capillary wedge pressure (PCW). After 0.2 mg pindolol intravenously the wave form of the wedge pressure is almost normalized. Simultaneously ST segment depression (lead

V6), indicating subendocardial ischaemic injury is reduced and the myocardial wall motion of the posterolateral segment is improved by echo from 3 mm to 7 mm. The recovery of function in ischaemic myocardial segment explains the relief of the functional subvalvular mitral competence.

function of the ischaemic myocardial segments is most consistent after beta blockade: the concordant course took place in 88% of instances. Follow-up studies of our patients several days later indicated that this recovery remained permanent in most of them, too. Thus the possibility that the acute reduction in the ST segment elevation resulted from progression of the ischaemic injury to necrosis (4, 20) instead of from an improvement in its degree, does not sound plausible in view of the simultaneous and significant ( $p < 0.0005$ ) recovery of the contractile function at the ischaemic myocardial zones after beta blockade. The same holds true, though less strictly with the directionally opposite changes after dopamine.

Particularly with minor ST segment deviations, or in nontransmural lesions with T wave changes only the sensitivity of the myocardial segment motion by echo clearly surpassed that of the electrocardiographic analysis in documenting the acute directional changes taking place at the ischaemic zones. Whether reduction of acute transmural ST elevations of a marked degree will be quantitatively and not only directionally correlated with simultaneous recovery of the myocardial segment function, remains to be clarified.

#### *Hemodynamic subset determining the selection of drug therapy*

Dopamine effectively enhanced the cardiac pump function without excessive tachycardia or ventricular arrhythmias in patients with acute myocardial infarction, as reported by others (16, 24, 25). However when used inappropriately in patients with moderate left heart failure only — not to mention complicated infarctions — if inotropic drugs may speedily and markedly increase ischaemic damage (22, 40). Both the ST segments and myocardial muscle mechanics acutely deteriorated, though initially even the ischaemic segments were responsive to the squeezing with inotropic demand, which has been demonstrated experimentally too (26, 68). However before long, with increasing ischaemia, this initial contractile improvement

tended to deteriorate once more, like experimentally (68). This unfavourable course can easily be avoided during drug therapy by observing the steadily increasing ST segments. In clinical practice this danger is most prevalent in patients who are hypotensive due to hypovolemia (8, 16, 17). This kind of occasional divergent course of the ST segments and myocardial mechanics also emphasizes the usefulness of combining the segmental motion and ST segments for monitoring the fate of myocardial ischaemia.

Any inotropic treatment has been condemned now and then in acute myocardial infarction. This straightforward opinion was not confirmed in the present study with dopamine. These data indicate that the initial hemodynamic state, i.e. failing or nonfailing of the left ventricle, modifies the effect of the dopamine infusion on the ischaemic zones. The same contrast is evident experimentally in uncomplicated myocardial infarction: inotropic drugs increase the infarct size in dogs, while in depressed ventricles the inotropic improvement of the pump function is possible without any increase in ischaemic injury (40, 71). Such data have been lacking with human myocardial infarction. We found that when inotropic support was directly needed, a moderate dose of dopamine augmented the critically low pump function of the patients, without killing the jeopardized ischaemic segments either electrocardiographically or mechanically (Fig. 6 and 9). Here the reduction of the wall stress by the markedly reduced size of the dilated left ventricle ( $p < 0.0005$ ) after dopamine would overcome the opposite effects of the heart rate and contractility on the myocardial oxygen consumption (40, 71). Acute dilatation of the left ventricle is common in myocardial infarction (52, 61).

Compared with isoproterenol, dopamine did not adversely affect the ST shifts in experimental myocardial infarction, perhaps due to favourable effect on regional coronary blood flow (43) and myocardial metabolism (73) while in another experimental setting the findings remained variable (34). The vasodilating properties of dopamine in small

### *Correlation between mechanical function of ischaemic myocardial segments and electrocardiographic ST segments after drug intervention*

The rapid changes of the contractile function in the ischaemic myocardial segments induced pharmacologically were compared directionally with the improvement or deterioration of the simultaneous electrocardiographic ST segment shifts. A discordant course was noted in only 18.8 %, or in 31 of 165 comparisons ( $p < 0.01$  sign test). With beta blockade alone, mechanical and electrical dissociation remained smaller 12.1 % (14 of 116 instances after multiple doses  $p < 0.01$ ) than after the inotropic stimulation with dopamine where a divergent course was rather common 23.5 % (8 of 34 instances). This is reasonable, since under inotropic demand even the ischaemic myocardium is often mechanically responsible (26 58 68) but unfortunately often at the expense of rapidly increasing ischaemia and later deterioration. For ethical reasons this stimulation was not continued in most patients except transiently in 4 of the 14 patients treated with both doses of dopamine this sequence of the initial improvement, contrasting with the deteriorating ST segments, was thereafter found to become replaced by mechanical deterioration. One of the two variables remained unchanged in 31 of the 195 comparisons. Thus complete agreement directionally was noted in 69 % and partial agreement in 83 % of all the comparisons ( $p < 0.01$  for both).

In 8 of 41 patients beta blockade induced a marked improvement of contractile function while the usually initially minor ST segment shift, mainly in nontransmural infarction remained less than 10%. Quantitatively no correlation was noted between the percentual reduction of the ST segments and the amount of improvement in the wall motion by beta blockade. Neither were ST segment shifts correlated quantitatively with changes in rate pressure product after beta blockade or dopamine although directionally the two variables were in excellent agreement.

### **Discussion**

#### *Detection of the fate of ischaemic myocardial segments without delay*

Since the myocardial infarction in general is larger in patients with pump failure and with serious ventricular arrhythmia than in those without them (2 7 27) any therapy to limit the amount of cardiac muscle killed during evolving infarction would seem to be extremely desirable. However measuring infarct size noninvasively in patients continues to be a problem. During application of the therapeutic intervention in particular at least a directional indication of the course of regional ischaemia should be known very rapidly. Otherwise, little hope remains for protecting ischaemic zones in an individual patient if the result is available only after several hours. This is the case, for instance, after attempts with enzymatic or myocardial imaging quantifications for ischaemia (22). The experience gained with the combined use of electrocardiographic ST segment mapping and the echocardiographic myocardial segmental mapping developed by us suggests the feasibility of using this technique for such studies. The method also seems to be quite accurate and very rapid.

#### *Validation of the ST segment shift as an indicator of ischaemic injury*

The degree of ST segment elevation in animals predicts the amount of later myocardial necrosis (13 63) although opinions differ somewhat (4 20). In man, there has been no direct evidence so far with other more specific methods that intervention reducing ST segment elevations really reflects a reversal of the ongoing ischaemic injury of the myocardium. Our data now indicate that the acute alterations of the ST segment shifts induced by pharmacological intervention are accompanied by directionally similar changes in the contractile function of the ischaemic myocardial segments. This applies to both the short term further elevation of the ST segments, and their significant reduction. The concordant reduction of the ST segment elevation with the recovery of contractile

Completely akinetic ischaemic segments were sometimes noted to recover almost normal contractility. This recruitment of the ischaemic segments ( $p < 0.0005$ ) clearly explains the preservation of adequate pump performance noted after beta blockade during the early stages of acute myocardial infarction. With the equivalent doses of 5 mg of practolol and 0.2 mg of pindolol, the latter seemed to reduce the signs of ischaemia more consistently and significantly. However the patient groups studied using practolol included more with pump failure, and most important, they had a longer duration of symptoms: an average of 23 hours in the practolol group and 15 hours in the pindolol group.

Interestingly enough, we have noted in preliminary studies that quite small doses of the beta blocking drugs used here produced most of the reduction noted in the signs of ischaemia. Increasing these doses of practolol and pindolol five-fold improved the ST segments or regional myocardial function only slightly but instead sometimes caused excessive bradycardia or univentricular block. This very small dosage is in clear contrast to the rather massive beta blockade usually used in animal experiments to reduce infarct size (13-60).

The ability to reduce acute myocardial ischaemia is greater during the first few hours of infarction. However it is not worthy that the various signs of ischaemia were highly significantly reduced by beta blockade much later too as this series included patients studied up to 48 hours from the onset of symptoms. This finding concurs with the concept of progressive, continuing course of acute myocardial infarction in man (2, 7, 12, 22, 26, 31, 42, 59, 66). Also, there is time to effectively protect ischaemic zones by therapy at least during the first two days after the onset of symptoms.

In conclusion, dopamine used with good judgement is sometimes very beneficial to patient with serious low output state complicating acute myocardial infarction. In contrast, the inappropriate use of dopamine

invariably increases ischaemia in nonfailing hearts. Small intravenous doses of beta blocking drugs seem to bring about a marked, safe reduction in the clinical, electrocardiographic and myocardial mechanical signs of ischaemia. Evidence was detected using direct echo visualization that the acute ST segment shifts indeed indicate a similar directional course in the mechanical function of the ischaemic myocardium in man. These noninvasive assessments may then prove to be of great clinical value in the characterization of myocardial ischaemia and infarction.

## References

1. Akayama, T., Hodges, M., Biddle, T. L., Zawrotny, B. & Vangelow, C.: Measurement of S-T segment elevation in acute myocardial infarction in man. Comparison of precordial mapping technique and the Frank vector system. *Amer J Cardiol* 36: 155, 1975.
2. Alonso, D. R., Schexel, S., Fox, M. & Killip, T. P.: Pathophysiology of cardiogenic shock. *Circulation* 48: 588, 1973.
3. Ashkenazi, J., Maroko, P. R., Leach, M. & Braunwald, E.: Usefulness of ST segment elevations as predictors of electrocardiographic signs of necrosis in patients with acute myocardial infarction. *Brit. Heart J* 39: 764, 1977.
4. Bodenheimer, M. M., Banks, V. S., Levine, R. & Helfant, K. H.: Temporal relation of epicardial electrographic, contractile and biochemical changes after acute coronary occlusion and reperfusion. *Amer J Cardiol* 37: 486, 1976.
5. Braunwald, E. & Maroko, P. R.: The reduction of infarct size — an idea whose time (for testing) has come. *Circulation* 50: 206, 1974.
6. Capone, R. J., Most, A. S. & Sydlík, P. A.: Precordial ST segment mapping. A sensitive technique for the evaluation of myocardial injury? *Chest* 67: 577, 1975.

doses (24) help one further to avoid an increased afterload, unfavourable to the failing left ventricle (62) In this series the systemic vascular resistance decreased by one fourth with dopamine. In clinical practice, use of moderate elevation of arterial pressure to increase a shock level coronary and peripheral circulation is often unavoidable (16 17 47 78) even with the modern use of vasodilators (10 62) In fact, the combined use of dopamine and nitroprusside evokes the best hemodynamic response in severe pump failure (10 44) Sometimes vasodilatory nervous reflexes cause marked hypotension (16 17) easily corrected by a small dopamine support.

However the presence of pump failure as such is not always enough to determine the use of inotropic therapy The easy monitoring of ST segment behavior is very helpful here in avoiding at least the unnecessary use of inotropic support. Excessive infusion rates, even in patients with severe pump failure could cause a later loss of stability in the ischaemic segments, obviously due to inordinately increasing vasoconstriction, contractility and heart rate (25) In this connection, the initial increase in the motion amplitude in the *uninvolved* segments also tended to become steady with the higher doses Whether this indicates excessive metabolic demand or myocardial segments being perfused by stenosed coronary arterial branches (53) remains unanswered.

**Beta blockade in acute myocardial infarction.** The small intravenous doses of the beta blocking drugs practolol and pindolol were hemodynamically safe, not only in the patients with uncomplicated infarction but also in those with moderate left heart failure. Left ventricular filling pressure and stroke volume did not change significantly after pindolol nor did the left ventricular cavity size change at all after each of these beta blocking drugs.

We selected these  $\beta$  blocking drugs due to their cardioselective and/or intrinsic sympathetic activities Such properties have been shown to depress contractility of the left ventricle less than propranolol (9) and the peripheral vasoconstriction which is unfavour-

able to the failing left ventricle (10 62) also remains less marked than with propranolol (41)

The favourable effect of practolol and pindolol on the reduction of myocardial mechanical and electrocardiographic signs of acute ischaemia was quite marked and consistent. Chest pain frequently disappeared at the same time as found by others (70) Reduction of the cardiac work is probably an obvious mechanism (5 30 38 46) (Fig. 9) while counteraction of the deleterious effects of increased catecholamine content at the ischaemic zones (21 57) and the better myocardial metabolism and perfusion may contribute to it as well (46 47) Experimentally Theroux et al. observed the same partial functional sparing of the marginal segments after propranolol (69)

Improvement of the ST segments was of the same order as reported by others with usually relatively larger doses of propranolol (15) pindolol (19) or practolol (55 56)

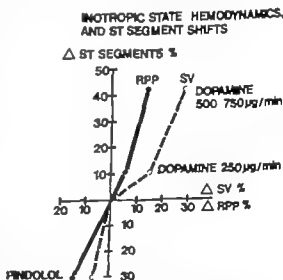


Fig 9 The mean increase decrease of the ST segment deviation by a beta stimulating (dopamine) or beta blocking drug (pindolol) was related to change of the rate pressure product which reflects myocardial oxygen consumption By the small dose of dopamine the stroke volume (SV) was increased relatively more than the rate pressure work with pindolol the decrease of stroke volume was insignificant

Completely akinetic ischaemic segments were sometimes noted to recover almost normal contractility. This "recruitment" of the ischaemic segments ( $p < 0.0005$ ) clearly explains the preservation of adequate pump performance noted after beta blockade during the early stages of acute myocardial infarction. With the equivalent doses of 5 mg of practolol and 0.2 mg of pindolol, the latter seemed to reduce the signs of ischaemia more consistently and significantly. However the patient groups studied using practolol included more with pump failure, and more important, they had a longer duration of symptoms: an average of 23 hours in the practolol group and 15 hours in the pindolol group.

Interestingly enough, we have noted in preliminary studies that quite small doses of the beta blocking drugs used here produced most of the reduction noted in the signs of ischaemia. Increasing these doses of practolol and pindolol five-fold improved the ST segments or regional myocardial function only slightly but instead sometimes caused excessive bradycardia or atrioventricular block. This very small dosage is in clear contrast to the rather massive beta blockade usually used in animal experiments to reduce infarct size (33-60).

The ability to reduce acute myocardial ischaemia is greater during the first few hours of infarction. However it is noteworthy that the various signs of ischaemia are highly significantly reduced by beta blockade much later too, as this series included patients studied up to 48 hours from the onset of symptoms. This finding concurs with the concept of "progressive, staggered" course of acute myocardial infarction in man (2, 7, 12, 22, 26, 31, 42, 59, 66). Also, there is time to effectively protect ischaemic zones by therapy at least during the first two days after the onset of symptoms.

In conclusion, dopamine used with good judgement is sometimes very beneficial to a patient with serious low output state complicating acute myocardial infarction. In contrast, the inappropriate use of dopamine

invariably increases ischaemia in nonfailing hearts. Small intravenous doses of beta blocking drugs seem to bring about marked, safe reduction in the clinical, electrocardiographic and myocardial mechanical signs of ischaemia. Evidence was detected using direct echo visualization that the acute ST segment shifts indeed indicate a similar directional course in the mechanical function of the ischaemic myocardium in man. These noninvasive assessments may then prove to be of great clinical value in the characterization of myocardial ischaemia and infarction.

## References

1. Akiyama, T. Hodges, M. Biddle, T. L., Zawrotny B. & Vangelow C. Measurement of S-T segment elevation in acute myocardial infarction in man. Comparison of a precordial mapping technique and the Frank vector system. *Amer J Cardiol* 36: 155 1975
2. Alonso, D. R., Scheidt, S., Fox, M. & Killip, T. Pathophysiology of cardiogenic shock. *Circulation* 48: 588 1973
3. Askenazi, J. Maroko, P. R., Leach, M. & Braunwald, E. Usefulness of ST segment elevations as predictors of electrocardiographic signs of necrosis in patients with acute myocardial infarction. *Br. Heart J* 39: 764 1977
4. Bodenheimer M. M., Banks, V. S., Levine, R. & Helfant, K. H. Temporal relation of epicardial electrographic, contractile and biochemical changes after acute coronary occlusion and reperfusion. *Amer J Cardiol* 37: 436 1976.
5. Braunwald, E. & Maroko, P. R. The reduction of infarct size — an idea whose time (for testing) has come. *Circulation* 50: 206, 1974
6. Capone, R. J. Moss, A. S. & Sydlík, P. A. Precordial ST segment mapping. A sensitive technique for the evaluation of myocardial injury? *Chest* 71: 577 1975

doses (24) help one further to avoid an increased afterload unfavourable to the failing left ventricle (62). In this series the systemic vascular resistance decreased by one fourth with dopamine. In clinical practice, use of moderate elevation of arterial pressure to increase a shock level coronary and peripheral circulation is often unavoidable (16, 17, 47, 78) even with the modern use of vasodilators (10, 62). In fact, the combined use of dopamine and nitroprusside evokes the best hemodynamic response in severe pump failure (10, 44). Sometimes vasodilatory nervous reflexes cause marked hypotension (16, 17) easily corrected by a small dopamine support.

However, the presence of pump failure as such is not always enough to determine the use of inotropic therapy. The easy monitoring of ST segment behavior is very helpful here in avoiding at least the unnecessary use of inotropic support. Excessive infusion rates, even in patients with severe pump failure, could cause a later loss of stability in the ischaemic segments, obviously due to inordinately increasing vasoconstriction, contractility and heart rate (23). In this connection, the initial increase in the motion amplitude in the *uninvolved* segments also tended to become steady with the higher doses. Whether this indicates excessive metabolic demand or myocardial segments being perfused by stenosed coronary arterial branches (53) remains unanswered.

**Beta blockade in acute myocardial infarction.** The small intravenous doses of the beta blocking drugs practolol and pindolol were hemodynamically safe, not only in the patients with uncomplicated infarction but also in those with moderate left heart failure. Left ventricular filling pressure and stroke volume did not change significantly after pindolol nor did the left ventricular cavity size change at all after each of these beta blocking drugs.

We selected these beta blocking drugs due to their cardioselective and/or intrinsic sympathetic activities. Such properties have been shown to depress contractility of the left ventricle less than propranolol (9) and the peripheral vasoconstriction which is unfavour-

able to the failing left ventricle (10, 62) also remains less marked than with propranolol (41).

The favourable effect of practolol and pindolol on the reduction of myocardial mechanical and electrocardiographic signs of acute ischaemia was quite marked and consistent. Chest pain frequently disappeared at the same time, as found by others (70). Reduction of the cardiac work is probably an obvious mechanism (5, 30, 38, 46) (Fig. 9) while counteraction of the deleterious effects of increased catecholamine content at the ischaemic zones (21, 57) and the better myocardial metabolism and perfusion may contribute to it as well (46, 47). Experimentally Theroux et al. observed the same partial functional sparing of the marginal segments after propranolol (69).

Improvement of the ST segments was of the same order as reported by others with usually relatively larger doses of propranolol (15), pindolol (19) or practolol (55, 56).

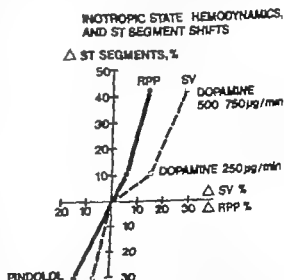


Fig. 9 The mean increase or decrease of the ST segment deviation by a beta stimulating (dopamine) or beta blocking drug (pindolol) was related to change of the rate pressure product which reflects myocardial oxygen consumption. By the small dose of dopamine the stroke volume (SV) was increased relatively more than the rate pressure work with pindolol the decrease of stroke volume was insignificant.

- Danung. *Excerpta Medica*, Amsterdam, 1972, p. 282.
- 28 Kerber R. E., Marcus, M. L. & Abboud, F. M. Echocardiography in experimentally-induced myocardial ischemia. *Amer J Med* 63 21 1977
- 29 Kitamura, K., Jorgensen, C. R., Gobel, F. L., Taylor H. L. & Wang, Y. Hemodynamic correlates of myocardial oxygen consumption during upright exercise. *J Appl. Physiol* 32 516 1972
30. Kjekshus, J. K.. How seals avoid myocardial infarction during diving. *Scand. J Clin. Lab Invest.* 37 95 1977
31. Kroonenberg, M. W. Hodges, M., Akiyama, T. Roberts, D. L., Ehrlich, D. A., Biddle, T. L. & Yu, P. N. ST-segment alterations after acute myocardial infarction. Relationship to clinical status. *Circulation* 54 756, 1976.
- 32 Lekven, J. Myocardial blood flow distribution. *Scand. J Clin. Lab. Invest.* 36 1 1976.
- 33 Lesch, M. Inotropic agents and infarct size. *Amer J Cardiol* 37 508 1976.
- 34 da Luz, P. Forrester, J. S., Wyatt, H. L., Waters, D. & Swan, H. J. C. Divergent effect of dopamine upon ischemic myocardium with partial and total coronary occlusion (abstr) *Amer J Cardiol* 37 130, 1976.
- 35 Madras, J. E. & Hood, W. B. J. Precoordial ST-segment mapping. 3. Stability of mps in the early phase of acute myocardial infarction. *Amer Heart J* 93 603 1977
- 36 Madras, J. E. Madras, N. E. & Hood, W. B. J. Precoordial ST-segment mapping. 2. Effects of oxygen inhalation on ischemic injury in patients with acute myocardial infarction. *Circulation* 53 411 1976
- 37 Madras, J. E., Venkateswaran, K. & Hood, W. B. Jr. Precoordial ST-segment mapping. 1. Clinical studies in the coronary care unit. *Circulation* 52 799 1975
38. Maroko P. R. & Braunwald, E. Modification of myocardial infarction size after coronary occlusion. *Ann. Intern. Med.* 79 720 1973
- 39 Maroko, P. R., Hillis, L. D. Muller J. E., T. Vazzi, L., Heyndrickx, G. R., Ray M., Chazelle M., Destanne, A., Askenazi, J. Salerno, J. Carpentier J. Resketmaya, N. A., Radvany P. Libby P. Razbc, D. S., Chazov E. I. Bobba, P. & Braunwald, E. Favourable effects of hyaluronidase on electrocardiographic evidence of necrosis in patients with acute myocardial infarction. *N Engl. J. Med.* 296 898, 1977
40. Maroko, P. R., Kjekshus, J. K., Sobel, B. E., Watanabe, T. Covell, J. W. Ross, J. Jr & Braunwald, E. Factors influencing infarct size following experimental coronary artery occlusions. *Circulation* 43 67 1971
- 41 Marshall R. J & Parratz, J. R. Comparative effects of propranolol and prazosin in the early stages of experimental canine myocardial infarction. *Brit. J Pharmacol* 57 295 1976
- 42 Mathey D. Blesfeld, W. Baur, H. & Hamrath, P. Creatine kinase release in acute myocardial infarction: correlation with clinical, electrocardiographic, and pathological findings. *Brit. Heart J* 37 1161 1975
- 43 McClenathan, J. H., Guyton, R. A., Breyer R. H., Newman, G. E. & Michaelis, L. L. The Effects of isoproterenol and dopamine on regional myocardial blood flow after stenosis of circumflex coronary artery. *J Thor Cardiovasc. Surg.* 73: 431 1977
- 44 Miller R. R., Williams, D. O. DeBiana, A. N. Amsterdam, E. A. & Mason, D. T. Ventricular afterload-reducing agents in congestive heart failure therapy. In *Congestive Heart Failure*, Ed. D. T. Mason, Yorke Medical Books, Dun-Donnelley Publ, New York, 1976, p. 343
- 45 Moss T. W. Subendocardial distribution of coronary blood flow and the



- 7 Caulfield, J B., Leimbach, R & Gold, H The relationship of myocardial infarct size and prognosis. *Circulation* 53 suppl 1 141 1976
- 8 Chatterjee, K. & Swan, H J C. Hemodynamic profile of acute myocardial infarction. In *Myocardial Infarction*, Ed E. Corday & H J C. Swan, Williams & Wilkins, Baltimore, 1973 p 51
- 9 Choquet, Y., Capote, R J Mason, D T., Amsterdam, E. A. & Zelis, R. Comparison of beta adrenergic blocking properties and negative inotropic effects of oxprenolol and propranolol in patients (abstr.) *Amer J Cardiol.* 29 257 1972
- 10 Cohn, J N & Franciosa, J A. Vasodilator therapy of cardiac failure. *New Engl J Med.* 297 254 1977
- 11 Corya, B Echocardiography in ischemic heart disease. *Amer J Med* 63 10 1977
- 12 Cox, J L., McLaughlin, V W., Flowers, N C & Horan, L G The ischemic zone surrounding acute myocardial infarction. Its morphology as detected by dehydrogenase staining *Amer Heart J* 76 650 1968
- 13 Ergin, M. A., Dastur G., Butt K. M H & Snuckey J H Prolonged epicardial mapping of myocardial infarction the effects of propranolol and intra aortic balloon pumping following coronary artery occlusion *J Thor Cardiovasc. Surg.* 72 892 1976
- 14 Feigenbaum H Echocardiography 2nd ed. Lea & Febiger Philadelphia, 1976
- 15 Gold, H K., Leimbach, R. C. & Maroko, P R. Propranolol induced reduction of signs of ischemic injury during acute myocardial infarction. *Amer J Cardiol.* 38 689 1976
- 16 Gunnar R. M Loeb, H. S. & Rahimtoola, H. S Shock in myocardial infarction Grune & Stratton Inc., New York, 1974
- 17 Heikkilä, J Pump failure and hemodynamic subsets in acute myocardial infarction. *Ann. Clin. Res.* 9 112, 1977
- 18 Heikkilä, J & Nieminen M. Echocardiographic detection, localization, and quantification of left ventricular asynergy in acute myocardial infarction. A correlative echo- and electrocardiographic study *Brit. Heart J* 37 46, 1975
- 19 Heindrich Meisner G & Harmjan, D Reduktion der myokardialen Ischämie beim akuten Infarkt durch Betablocker (Pindolol) *Z. Kardiologie* 66 211 1977
- 20 Heng, M. K., Singh B N Norris, R. M., John M. B & Elliot, R. Relationship between epicardial ST-segment elevation and myocardial ischemic damage after experimental coronary artery occlusion in dogs. *J Clin. Invest.* 58 1317 1976
- 21 Herbaczynska-Cedro A. The influence of adrenaline secretion on the enzymes in heart muscle after coronary occlusion in dog. *Cardiovasc. Res.* 4 168 1970
- 22 Hultis, L. D & Braunwald, E. Myocardial ischemia. *New Engl. J Med* 296 971 1977
- 23 Holland, R. P & Arnsdorf M F Solid angle theory and the electrocardiogram physiological and quantitative interpretations. *Progr Cardiovasc. Res.* 19 431 1977
- 24 Holloway E. L., Stinson, E. B Derby, G C & Harrison, D C Action of drugs in patients early after cardiac surgery I Comparison of isoproterenol and dopamine. *Amer J Cardiol.* 35 656, 1975
- 25 Holzer J Karlner J S., O'Rourke, R. A Pitt, W & Ross, J., Jr Effectiveness of dopamine in patients with cardiogenic shock. *Amer Cardiol* 32 79 1973
- 26 Hood, W B., Jr ST-segment mapping in ischemia and infarction. *Circulation* 53 suppl 1 93 1976
- 27 Jewitt, D E. & Singh, B N Beta adrenergic blockade in acute myocardial infarction. In *Textbook of Coronary Care*, Ed. L. E. Meltzer & A. J

63. Sasayama, S., Franklin, D. Ross, J. Jr, Kemper W S & McKown, D. Dynamic changes in left ventricular wall thickness and their use in analyzing cardiac function in the conscious dog. A study based on a modified ultrasonic technique. *Amer J Cardiol* 38: 870, 1976.
66. Selwyn, A. P., Ogunro, E. A. & Shillingford, J. P. Natural history and evaluation of ST segment changes and MB CK release in acute myocardial infarction. *Brit. Heart J* 39: 988, 1977.
67. Stone, K. I., Fogelman, A. M., Kattus, A. A., Beckberg, G. D. & Tillsch, J. H. Pathophysiology of myocardial infarction. *Ann. Intern. Med.* 87: 75, 1977.
68. Theroux, P., Franklin, D. Ross, J. J. & Kemper W S. Regional myocardial function during acute coronary artery occlusion and its modification by pharmacologic agents in dog. *Circ. Res.* 35: 896, 1974.
69. Theroux, P., Ross, J. J., Franklin, D., Kemper W S. & Sasayama, S. Regional myocardial function in the conscious dog during acute coronary occlusion and responses to morphine, propranolol, nitroglycerin, and lidocaine. *Circulation* 53: 302, 1976.
70. Waagstein, F. & Hjalmarson, A. C., Effect of cardioselective betablockade on heart function and chest pain in acute myocardial infarction. *Acta Med. Scand., suppl.* 587: 193, 1975.
71. Watanabe, T., Covell, J. W., Maroko P. R., Braunwald, E. & Ross, J. Jr. Effects of increased arterial pressure and positive inotropic agents on the severity of myocardial ischemia in the acutely depressed heart. *Amer J Cardiol.* 30: 371, 1972.
72. Weiner J. M., Apstein, C. S., Arthur J. H. & Hood, W. B. Jr. Persistence of myocardial injury following brief periods of coronary occlusion. *Amer J Cardiol.* 33: 77, 1974.
73. Winslow E., Loeb, H., Rahimtoola, S. H., Rosen, K. & Gunnar R. Transmyocardial lactate metabolism during treatment of shock with catecholamines. *Circulation* 42: suppl 3: 207, 1970.
74. Wyatt, H. L., Forrester J. S., Tyberg, J. V., Goldner S., Logan, S. E., Parmley W W & Swan, H. J. C. Effect of graded reductions in regional coronary perfusion on regional and total cardiac function. *Amer J Cardiol.* 36: 185, 1975.

- effect of antianginal drugs *Circ Res.* 30 621 1972.
- 46 Mueller H R. & Ayres, S M The role of propranolol in the treatment of acute myocardial infarction. *Progr Cardiovasc. Dis.* 19 405 1977
- 47 Mueller H R., Ayres, S M., Conklin E. F., Gianelli S Jr., Mazzara, J T., Grace, W T & Nealon, T F., Jr The effects of intra aortic counterpulsation on cardiac performance and metabolism in shock associated with acute myocardial infarction *J Clin Invest.* 50 1885 1971
- 48 Muller J E., Maroko P R. & Braunwald E. Evaluation of precordial electrocardiographic mapping as a means of assessing changes in myocardial ischemic injury *Circulation* 52 16, 1975
- 49 Nieminen, M Normal left echoventriculography *Ann Clin. Res.* 7 1 1975
- 50 Nieminen, M S Echoventriculography in chronic coronary heart disease Correlation with single-plane cineangiography of the left ventricle. *Eur J Cardiol* 5 343 1977
- 51 Nieminen M. S Applications of multidirectional echocardiography in myocardial infarction Academic dissertation, Helsinki 1977
- 52 Nieminen, M. & Heikkilä, J Echoventriculography in acute myocardial infarction. II Monitoring of left ventricular performance. *Brit. Heart J* 38 271 1976
- 53 Nieminen, M. & Heikkilä, J Echoventriculography in acute myocardial infarction. III Clinical correlations and implication of the noninfarcted myocardium *Amer J Cardiol* 38 1 1976
- 54 Nieminen, M. & Heikkilä J The accuracy and usefulness of echoventriculography in acute myocardial infarction *Acta Med. Scand.* (in print)
- 55 Norris, R. M., Barrett Boyes, C., Heng, M K. & Singh, B N Failure of ST segment elevation to predict severity of acute myocardial infarction. *Brit. Heart J* 38 85 1976
- 56 Pelides, L. J., Reid, D S. Thomas, M. & Shillingford, J P Inhibition by  $\beta$ -blockade of the ST segment elevation after acute myocardial infarction in man. *Cardiovasc. Res.* 6 295 1972.
- 57 Popov V G., Lazutin, V K., Mintrov N K., Zhelnov V V & Svirskikh, A. I Noradrenaline and adrenaline content in different sections of the heart in patients deceased due to myocardial infarction. *Kardiologia* 15 102, 1975
- 58 Ramanathan, K. B Bodenheimer M M., Banks, V S., Raina, S & Helfant, R. H Contrasting effects of dopamine and isoproterenol in experimental myocardial infarction. *Amer J Cardiol* 39 413 1977
- 59 Reid, P R., Taylor D R., Kelly D T Weisfeldt, M L., Humphries, J N Ross, R. S & Pitt, B Myocardial-infarct extension detected by precordial ST-segment mapping. *New Engl. J Med* 290 123 1974
- 60 Reimer K. A Rasmussen M. M. & Jennings, R. B. Reduction by propranolol of myocardial necrosis following temporary coronary occlusion in dogs. *Circ. Res.* 33 353 1973
- 61 Rigo, P., Murray M., Strauss, H W Taylor D Kelly D Weisfeldt, M & Pitt, B. Left ventricular function in acute myocardial infarction evaluated by gated scintiphotography *Circulation* 50 678 1974
- 62 Ross, J Jr Afterload mismatch and preload reserve a conceptual framework for the analysis of ventricular function. *Progr Cardiovasc. Dis.* 18 255 1976.
- 63 Ross, J., Jr Electrocardiographic ST segment analysis in the characterization of myocardial ischemia and infarction *Circulation* 53 suppl. 1 73 1976
- 64 Ross, J Jr & Franklin, D Analysis of regional myocardial function, dimensions, and wall thickness in the characterization of myocardial ischemia and infarction. *Circulation* 53 suppl 1: 88 1976

Table 1 ST-T data and echocardiographic variables in 24 male patients with previous myocardial infarction. Figures are mean  $\pm$  1 SD

Variable	All MI N=4	Normal N=49	Ant. MI N=14	Inf. MI N=8	One MI N=17	$\geq 2$ MI N=7	NYHA 1-2 N=17	NYHA 3-4 N=7
Q <sub>3/1</sub> m	511 $\pm$ 23	505 $\pm$ 16	507 $\pm$ 26	520 $\pm$ 18	509 $\pm$ 24	516 $\pm$ 19	518 $\pm$ 18	X 496 $\pm$ 28
LVETI mm	375 $\pm$ 25	X 388 $\pm$ 12	369 $\pm$ 28	387 $\pm$ 15	374 $\pm$ 27	375 $\pm$ 18	385 $\pm$ 16	3 X 350 $\pm$ 28
PEP mm	116 $\pm$ 11	3 X 94 $\pm$ 12	170 $\pm$ 9	X 110 $\pm$ 11	115 $\pm$ 12	119 $\pm$ 6	113 $\pm$ 11	X 123 $\pm$ 8
PEP/LVET $\times 10^3$	448 $\pm$ 82	3 X 343 $\pm$ 49	475 $\pm$ 90	406 $\pm$ 66	448 $\pm$ 93	451 $\pm$ 47	416 $\pm$ 62	2 X 526 $\pm$ 77
S-ASAT U/l	228 $\pm$ 143	—	274 $\pm$ 149	X 140 $\pm$ 97	243 $\pm$ 159	195 $\pm$ 95	196 $\pm$ 146	291 $\pm$ 144
-R mm	56 $\pm$ 27	—	49 $\pm$ 19	X 69 $\pm$ 34	50 $\pm$ 22	72 $\pm$ 28	60 $\pm$ 29	47 $\pm$ 17
-Q mm	29 $\pm$ 20	—	37 $\pm$ 21	2 X 14 $\pm$ 8	28 $\pm$ 19	33 $\pm$ 44	28 $\pm$ 19	33 $\pm$ 22
-ST mm	54 $\pm$ 3	—	64 $\pm$ 3	44 $\pm$ 3	57 $\pm$ 3	46 $\pm$ 3	44 $\pm$ 2	X 79 $\pm$ 4
Log $\frac{-R \times 10^4}{SQ \times -ST}$	2.67 $\pm$ 0.66	—	2.48 $\pm$ 0.67	X 3.07 $\pm$ 0.41	2.67 $\pm$ 0.66	2.69 $\pm$ 0.71	2.84 $\pm$ 0.68	X 2.21 $\pm$ 0.30

level of significance: X  $\Rightarrow p < 0.05$  2 X  $\Rightarrow p < 0.01$  3 X  $\Rightarrow p < 0.001$  See text for explanation of abbreviations.

# Left ventricular function after myocardial infarction. Relation between systolic time intervals and quantitative ischaemic ECG changes

John Godtfredsen, Peter Kryger and Henrik Lublin

Dept. of Medicine, Kommunehospitalet, COPENHAGEN DENMARK

## Abstract

Twentyfour male patients with sustained myocardial infarction (MI) were studied with 12 lead ECG and systolic time intervals (STI) 5 months after the acute episode. From the ECGs were calculated the summed voltages of the R wave ( $\Sigma R$ ) the Q wave ( $\Sigma Q$ ) and the ST segment deviation ( $\Sigma ST$ ). These ischaemic ECG variables were correlated with the STI parameters of left ventricular function LVETI, PEP and PEP/LVET. Statistically significant regression equations relating the ECG changes to the STI variables were found in anterior MI for  $\Sigma ST$  in the entire series, but not in inferior MI. Thus a simple and rapid inspection of the resting 12 lead ECG gives an indirect but reliable quantitative estimate of left ventricular function in patients with a sustained myocardial infarction.

Experimental studies have shown a relation between QRS changes in the ECG and the size of myocardial infarction (MI) (11-21). As the extent of myocardial damage after MI determines the impairment of left ventricular (LV) function (14-20, 25) a correlation between QRS changes and the LV performance would be expected. Linear correlation between the summed R wave voltages ( $\Sigma R$ ) and the number of Q waves (Q index) and the angiographically determined LV ejection fraction has been reported

in patients with chronic ischaemic heart disease (2, 4). This study looked for a quantitative correlation between the LV performance as reflected by various systolic time intervals (STI) and ischaemic ECG changes ( $\Sigma R$ ,  $\Sigma Q$  and  $\Sigma ST$ ) in a group of patients with previous MI.

## Material and methods

The patients were 24 men aged 45-71 years (mean 57.5) with a definite MI in their history. The time from the last MI to the ECG and STI recording was in median 5 months, range 1-17 months. Fourteen patients had anterior MI, 8 had inferior MI and 2 had both. Seventeen had one MI and 7 had 2-3 MIs. According to the N.Y.H.A. classification of heart diseases, 17 were in class 1-2, and 7 were in class 3-4.

The patients were studied on their usual medication but with beta-blocker therapy withheld for at least 2 days. A conventional ECG (12 leads) and the STI variables were recorded. The patients were resting supine and Elema Schöndander phonomicrophone EMT 25B with amplifier EMT 22 was used for the carotid tracing, a transducer EMT 510C (time constant 4 sec) and the Mungo-graf 34 3-channel jet ink writer were employed.

The ECG lead II phonocardiogram and carotid pulse tracing were recorded simultaneously at a paper speed of 100 mm per second. The ECG calibration was carefully

Table III Anterior MI (N = 14) Regression equations correlating STI variables with ischaemic ECG changes

		r	P
LVETI	$= -4.820 \Delta ST + 398$	-0.61	< 0.05
PEP	$= 1.612 \Delta ST + 109$	0.62	< 0.05
PEP/LVET $\times 10^3$	$= 17.615 \Delta ST + 363$	0.59	< 0.05
PEP	$= -0.266 \Delta R + 133$	-0.56	< 0.05
PEP/LVET $\times 10^3$	$= -2.646 \Delta R + 605$	-0.56	< 0.05
STI variables vs. $\Delta Q$ and index No significant correlation.			

Table IV Patients with 1 MI (N = 17) Regression equations correlating STI variables with ischaemic ECG changes

		P	
LVETI	$= -4.450 \Delta ST + 399$	-0.56	< 0.01
PEP	$= 1.612 \Delta ST + 106$	0.47	< 0.10
PEP/LVET $\times 10^3$	$= 16.7 \Delta ST + 354$	0.61	< 0.01
STI variables vs. $\Delta R$ and $\Delta Q$ No significant correlation			

Table V Patients with  $\geq 2$  MI (N = 7) Regression equations correlating STI variables with ischaemic change on ECG

		r	P
LVETI	$= 0.570 \Delta R + 334$	0.89	< 0.01
PEP/LVET $\times 10^3$	$= -1.4 \Delta R + 548$	-0.81	< 0.05
PEP	$= 0.232 \Delta Q + 112$	0.80	< 0.05
STI variables $\Delta ST$ No significant correlation			

adjusted to 10 mm deflection = 10 mV. From the ECG baseline ( $\approx T-P$  segment) the deflections of the Q wave, the R wave and the maximum ST segment elevation or depression were measured to the nearest 0.5 mm in every lead and summed to give the  $\Sigma R$ ,  $\Sigma Q$  and the  $\Sigma ST$  respectively in millimetres. The  $QS_2$  and LVET intervals were measured to the nearest 5 milliseconds, and the PEP and PEP/LVET were calculated in the usual manner. The heart rate was determined and used for the calculation of the corrected value LVETI. This calculation used correction factors derived from STI measurements on 49 normal men studied in our laboratory. As part of the acute diagnosis of MI the serum aspartate aminotransferase (S-ASAT) was determined and its peak value taken as an approximate marker of myocardial damage.

Regression equations and correlation coefficients ( $r$ ) were calculated and  $t$  tested using standard statistical methods.

## Results

Table I shows the findings in and the differences between the various subgroups of patients. Except for the  $QS_2I$  the STI variables are clearly abnormal compared with

the control group. Between anterior MI and inferior MI significant differences are seen in PEP in S-ASAT and as could be expected in  $\Sigma R$ , and  $\Sigma Q$ . No significant differences are seen between the patients with one MI and those with  $\geq 2$  MIs. Between the clinical markers of left ventricular dysfunction the NYHA class 1-2 and 3-4 significant differences in all the STI variables are seen. This difference is also reflected in  $\Sigma ST$  and in the compound ECG index ( $\text{Log } \frac{\Sigma R \times 10^3}{\Sigma Q \times \Sigma ST}$ ). Table II shows the

correlation between left ventricular (LV) function, as assessed by the LVETI, PEP, PEP/LVET and the calculated ECG variables  $\Sigma R$ ,  $\Sigma ST$  and the compound indices in all the MI patients. The  $\Sigma R$  and  $\Sigma Q$  show no significant correlation with the LV function, whereas the compound indices show a weak but significant correlation with PEP/LVET. Table III, IV and V show the same correlations in the various patient subgroups. In patients with one MI no significant correlation existed between peak S-ASAT values during the acute MI phase (= a possible marker of infarct size) and LV function, as judged by the STI variables, or by the ECG variables  $\Sigma R$ ,  $\Sigma Q$  and  $\Sigma ST$  (Table VI).

Table II: All MI patients ( $N = 24$ ). Regression equations correlating STI variables with ischaemic ECG changes

		$r$	$P$
LVETI	$= -3.267 \Sigma ST + 392$	-0.45	< 0.05
PEP	$= 1.406 \Sigma ST + 109$	0.45	< 0.05
PEP/LVET $\times 10^3$	$= 1.3 \Sigma ST + 379$	0.54	< 0.01
PEP/LVET $\times 10^3$	$= -17.6 \text{ Index}_1 + 495$	-0.43	< 0.05
PEP/LVET $\times 10^3$	$= -59.0 \text{ Index}_2 + 607$	-0.47	< 0.05
STI variables vs $\Sigma R$ and $\Sigma Q$ . No significant correlation			

$$\text{Index}_1 = \frac{\Sigma R}{\Sigma Q + \Sigma ST}$$

$$\text{Index}_2 = \text{Log } \frac{\Sigma R \times 10^3}{\Sigma Q \times \Sigma ST}$$

Table III Anterior MI (N = 14) Regression equations correlating STI variable with ischaemic ECG changes

		r	P
LVETI	= - 4.820 $\Sigma$ ST + 398	-0.61	<0.05
PEP	= 1.612 $\Sigma$ ST + 109	0.62	<0.05
PEP/LVET $\times 10^3$	= 17.615 $\Sigma$ ST + 363	0.59	<0.05
PEP	= - 0.266 $\Sigma$ R + 133	-0.56	<0.05
PEP/LVET $\times 10^3$	= - 2.646 $\Sigma$ R + 605	-0.56	<0.05
STI variables vs. $\Sigma$ Q and index. No significant correlation.			

Table IV Patients with 1 MI (N = 17). Regression equations correlating STI variables with ischaemic ECG changes

		r	P
LVETI	= - 4.450 $\Sigma$ ST + 399	-0.56	<0.01
PEP	= 1.612 $\Sigma$ ST + 106	0.47	<0.10
PEP/LVET $\times 10^3$	= 16.7 $\Sigma$ ST + 354	0.61	<0.01
STI variables $\Sigma$ R and $\Sigma$ Q. N significant correlation			

Table V Patients with  $\geq 2$  MI (N = 7) Regression equations correlating STI variables with ischaemic changes in ECG

		r	P
LVETI	= 0.570 $\Sigma$ R + 334	0.89	<0.01
PEP/LVET $\times 10^3$	= - 1.4 $\Sigma$ R + 548	-0.81	<0.05
PEP	= 0.232 $\Sigma$ Q + 112	0.80	<0.05
STI variables $\Sigma$ ST. No significant correlation			



adjusted to 10 mm deflection = 1.0 mV. From the ECG baseline (=T-P segment) the deflections of the Q wave, the R wave, and the maximum ST segment elevation or depression were measured to the nearest 0.5 mm in every lead and summed to give the  $\Sigma R$ ,  $\Sigma Q$  and the  $\Sigma ST$  respectively in millimetres. The  $QS_2$  and LVET intervals were measured to the nearest 5 milliseconds and the PEP and PEP/LVET were calculated in the usual manner. The heart rate was determined and used for the calculation of the corrected value LVET<sub>1</sub>. This calculation used correction factors derived from STI measurements on 49 normal men studied in our laboratory. As part of the acute diagnosis of MI the serum aspartate aminotransferase (S-ASAT) was determined, and its peak value taken as an approximate marker of myocardial damage.

Regression equations and correlation coefficients ( $r$ ) were calculated and  $t$  tested using standard statistical methods.

## Results

Table I shows the findings in and the differences between the various subgroups of patients. Except for the  $QS_2$  the STI variables are clearly abnormal compared with

the control group. Between anterior MI and inferior MI significant differences are seen in PEP in S-ASAT and as could be expected, in  $\Sigma R$ , and  $\Sigma Q$ . No significant differences are seen between the patients with one MI and those with  $\geq 2$  MIs. Between the clinical markers of left ventricular dysfunction, the NYHA class 1-2 and 3-4 significant differences in all the STI variables are seen. This difference is also reflected in  $\Sigma ST$  and in the compound ECG-

index ( $\text{Log } \frac{\Sigma R \times 10^3}{\Sigma Q \times \Sigma ST}$ ). Table II shows the correlation between left ventricular (LV) function, as assessed by the LVET<sub>1</sub>, PEP, PEP/LVET and the calculated ECG variables  $\Sigma R$ ,  $\Sigma ST$  and the compound indices in all the MI patients. The  $\Sigma R$  and  $\Sigma Q$  show no significant correlation with the LV function, whereas the compound indices show a weak, but significant correlation with PEP/LVET. Table III, IV and V show the same correlations in the various patient subgroups. In patients with one MI no significant correlation existed between peak S-ASAT values during the acute MI phase (= a possible marker of infarct size) and LV function, as judged by the STI variables, or by the ECG variables  $\Sigma R$ ,  $\Sigma Q$  and  $\Sigma ST$  (Table VI).

Table II All MI patients ( $N = 24$ ) Regression equations correlating STI variables with ischaemic ECG changes

		$r$	$P$
LVET <sub>1</sub>	$= -3.267 \Sigma ST + 392$	-0.45	< 0.05
PEP	$= 1.406 \Sigma ST + 109$	0.45	< 0.05
PEP/LVET $\times 10^3$	$= 1.3 \Sigma ST + 379$	0.54	< 0.01
PEP/LVET $\times 10^3$	$= -17.6 \text{ Index}_1 + 495$	-0.43	< 0.05
PEP/LVET $\times 10^3$	$= -59.0 \text{ Index}_2 + 607$	-0.47	< 0.05
STI variables vs $\Sigma R$ and $\Sigma Q$ No significant correlation			

$$\text{Index}_1 = \frac{\Sigma R}{\Sigma Q + \Sigma ST} \quad \text{Index}_2 = \text{Log } \frac{\Sigma R \times 10^3}{\Sigma Q \times \Sigma ST}$$

Table III Anterior MI (N = 14) Regression equations correlating STI variables with ischaemic ECG changes

		r	p
LVETI	$= -4.820 \Delta ST + 398$	-0.61	< 0.05
PEP	$= 1.612 \Delta ST + 109$	0.62	< 0.05
PEP/LVET $\times 10^3$	$= 17.615 \Delta ST + 363$	0.59	< 0.05
PEP	$= -0.266 \Delta R + 133$	-0.56	< 0.05
PEP/LVET $\times 10^3$	$= -2.646 \Delta R + 605$	-0.56	< 0.05
STI variables vs. $\Delta Q$ and index No significant correlation.			

Table IV Patients with 1 MI (N = 17) Regression equations correlating STI variables with ischaemic ECG changes

		r	p
LVETI	$= -4.450 \Delta ST + 399$	-0.56	< 0.01
PEP	$= 1.612 \Delta ST + 106$	0.47	< 0.10
PEP/LVET $\times 10^3$	$= 16.7 \Delta ST + 354$	0.61	< 0.01
STI variables $\Delta R$ and $\Delta Q$ No significant correlation			

Table V Patients with  $\geq 2$  MI (N = 7) Regression equations correlating STI variable with ischaemic change in ECG

		r	p
LVETI	$= 0.570 \Delta R + 334$	0.89	< 0.01
PEP/LVET $\times 10^3$	$= -1.4 \Delta R + 548$	-0.81	< 0.05
PEP	$= 0.232 \Delta Q + 112$	0.80	< 0.05
STI variables $\Delta ST$ No significant correlation			

Table VI Correlation matrix for peak S-ASAT values vs STI and ECG variables in 17 patients with 1 MI

	r"	
LVETI	0.22	
PEP	-0.32	
PEP/LVET	-0.34	All are
ΣR	-0.22	n.s.
ΣQ	-0.18	
ΣST	0.35	

Of the 13 patients with  $\Sigma R > 55$  mm, 31 % had  $PEP/LVET > 0.44$  (= normal value  $\pm 2SD$ ) in contrast to the 11 patients with  $\Sigma R \leq 55$  mm of whom 72 % had a  $PEP/LVET \geq 0.44$ . However this difference is not statistically significant.

## Discussion

Ischaemic ECG changes in man have been related to coronary artery disease as judged by arteriography (10, 17, 26, 27) to LV contractile patterns (the Q wave) (5, 18) to myocardial metabolic derangement, and to myocardial blood flow (the ST segment) (12, 22, 23) and more recently to LV function, as determined by the ejection fraction (the R wave and Q index) (2, 4).

The amount of necrotic myocardium after an acute myocardial infarction directly determines the degree of functional impairment of the left ventricle (14, 20, 25). If information contained in the standard 12 lead ECG is quantitatively or directionally related to parameters reliably estimating LV function, we then have a simple and noninvasive means for estimating the amount of myocardial damage and the size of an MI. The work of some clinical investigators has made it probable that such LV functional information is present in the 12 lead ECG. Askenazi et al (2) showed a weak but statistically significant correlation between the angiographically determined LV ejection fraction and the summed R wave voltage of 8 ECG leads. Other authors reported the number of Q waves in a precordial map to be correlated

to the ejection fraction and the extent of LV segmental dyssynergy (4, 18). As with the clinical usefulness of the ST segment changes in the ECG in the acute phase of MI as markers of acute myocardial ischaemia or infarct size, we should not expect a perfect linear correlation but directionally similar changes in the ECG markers of myocardial tissue damage and other pertinent variables, invasive or noninvasive, of LV function (6, 8).

Measurement of the systolic time intervals has been widely applied in chronic ischaemic heart disease and was reported by many workers to give a reliable quantitative estimate of the LV function when compared with invasive parameters (1, 9, 13, 15, 16, 24). From the work by Eddleman et al (7) it seems that elevated values of  $PEP/LVET$  exceeding 0.440 almost always denote decreased LV ejection fraction to be less than 50 %.

In this study we found a weak but statistically significant correlation between the noninvasively determined LV function, as expressed by STI variables, and possible quantitative ECG markers of myocardial necrosis  $\Sigma R$ ,  $\Sigma Q$  and  $\Sigma ST$ . We recognize that STI measurements describing LV function are very indirect and that the correlation with the ECG variables is still far from being a direct expression of LV function, but our findings support the use of  $\Sigma R$  and Q index as indicators of LV performance, as found by others (2, 4) except that the  $\Sigma Q$  in our study was the poorest marker.

The use in this study of compound ECG indices (see Table II) did not improve the correlation with the STI variables, but served as an indicator separating the NYHA class 1-2 from the class 3-4 patients, thus confirming a relation between quantitative ECG variables and clinical markers of the severity of myocardial damage.

The correlation between the  $\Sigma ST$ ,  $\Sigma R$ , and the various STI variables in anterior MI indicates that, although not a perfect quantitative relation, the standard ECG is a clinically useful indicator of myocardial damage.

in inferior MI, no correlation was found in this study. But it is possible that the use of only the pertinent ECG leads II, III and aVF for the ST and STQ calculation and a larger patient series might show results similar to those in the anterior MI group.

Patients with 1 MI did not show any correlation between S-ASAT and ischaemic ECG changes or STI variables: this agrees with the findings of Norma et al (19) that no relation exists in the acute MI phase between enzyme levels and STST changes or clinical or haemodynamic variables. However, persisting ST segment elevations, as expressed by the STST in this study, apparently correlate with LVETI and PEP/LVET (Table IV).

In the group of 7 patients with  $\geq 2$  MIs, the correlation between, on one hand, the STI variables and, on the other, ST and STQ was excellent, despite there not being any significant difference between the radiological variables (STI or ECG) in this group and the group with 1 MI (Table V).

Although not significant, a ST  $< 55$  mm is associated with PEP/LVET exceeding 0.44 and thus probably a LV ejection fraction  $< 50\%$ . A similar relation was found by Askenazi et al (2).

The relation between the ECG variables and LV function also suggests a possible role of ST and STQ as markers of possible results of various infarct-limiting interventions (3, 11).

The immediate clinical implication of this study is that simple and rapid inspection of standard 12 lead ECG gives an indirect but reliable quantitative estimate of the LV function in patients with previous myocardial infarction.

## References

- 1 Ahmed, S. S., Levinson, G. E., Schwartz, C. J. & Ettinger, P. O. Systolic time intervals as measures of the contractile state of the left ventricular myocardium in man. *Circulation* 46: 559-1972.
- 2 Askenazi, J., Freedman, W. B., Cohn, P. F., Braunwald, E. & Parina, A. F. The predictive value of the QRS complex in assessment of left ventricular function. *Circulation* 53 & III suppl II: 125-1976.
- 3 Askenazi, J., Maroko, P. R., Leach, M. & Braunwald, E. Usefulness of ST segment elevations as predictors of electrocardiographic signs of necrosis in patients with acute myocardial infarction. *Brit. Heart J.* 39: 764-1977.
- 4 Awar, N. A., Miller, R. R., Zakandem, V., Janzen, D. A., Amsterdam, E. A. & Mason, D. T. Noninvasive assessment of cardiac function and ventricular dyssynergy by precordial Q wave mapping in anterior myocardial infarction. *Circulation* 55: 833-1977.
- 5 Bodenheimer, M. M., Banks, V. S. & Helfant, R. H. Q waves and ventricular asynergy: Predictive value and hemodynamic significance of anatomic localization. *Amer. J. Cardiol.* 35: 615-1975.
- 6 Braunwald, E. & Maroko, P. R. ST segment mapping, realistic and unrealistic expectations. *Circulation* 54: 529-1976.
- 7 Eddleman, E. E., Swartzell, R. H., Bancroft, W. H., Baldone, J. C. & Tucker, M. S. The use of the systolic time interval for predicting left ventricular ejection fraction in ischemic heart disease. *Amer. Heart J.* 93: 450-1977.
- 8 Fozzard, H. A. & DacCuppa, D. S. ST segment potentials and mapping: theory and experiments. *Circulation* 54: 533-1976.
- 9 Garrard, C. L., Weisler, A. M. & Dodge, H. T. The relationship of alterations in systolic time intervals to ejection fraction in patients with cardiac disease. *Circulation* 42: 455-1970.
- 10 Herman, M. V., Elliot, W. C. & Gorlin, R. An electrocardiographic, anatomic, and metabolic study of zonal myocardial ischemia in coronary heart disease. *Circulation* 35: 834-1967.
- 11 Hillis, L. D., Askenazi, J., Braunwald, E., Radovany, P., Muller, J. E., Fish-

Table VI Correlation matrix for peak S ASAT values v STI and ECG variables in 17 patients with 1 MI

	r	
LVETI	0.22	
PEP	-0.32	
PEP/LVET	-0.34	All are
$\Sigma R$	-0.22	n.s.
$\Sigma Q$	-0.18	
$\Sigma ST$	0.35	

Of the 13 patients with  $\Sigma R > 55$  mm 31 % had  $PEP/LVET > 0.44$  (=normal value  $\pm 2SD$ ) in contrast to the 11 patients with  $\Sigma R \leq 55$  mm of whom 72 % had a  $PEP/LVET \geq 0.44$ . However this difference is not statistically significant.

## Discussion

Ischaemic ECG changes in man have been related to coronary artery disease, as judged by arteriography (10 17 26 27) to LV contractile patterns (the Q wave) (5 18) to myocardial metabolic derangement, and to myocardial blood flow (the ST segment) (12, 22, 23) and more recently to LV function, as determined by the ejection fraction (the R wave and Q index) (2, 4).

The amount of necrotic myocardium after an acute myocardial infarction directly determines the degree of functional impairment of the left ventricle (14 20 25). If information contained in the standard 12 lead ECG is quantitatively or directionally related to parameters reliably estimating LV function, we then have a simple and noninvasive means for estimating the amount of myocardial damage and the size of an MI. The work of some clinical investigators has made it probable that such LV functional information is present in the 12 lead ECG. Askenazi et al (2) showed a weak but statistically significant correlation between the angiographically determined LV ejection fraction and the summed R wave voltage of 8 ECG leads. Other authors reported the number of Q waves in a precordial map to be correlated

to the ejection fraction and the extent of LV segmental dyssynergy (4 18). As with the clinical usefulness of the ST segment changes in the ECG in the acute phase of MI as markers of acute myocardial ischaemia or infarct size, we should not expect a perfect linear correlation, but directionally similar changes in the ECG markers of myocardial tissue damage and other pertinent variables, invasive or noninvasive, of LV function (6, 8).

Measurement of the systolic time intervals has been widely applied in chronic ischaemic heart disease and was reported by many workers to give a reliable quantitative estimate of the LV function when compared with invasive parameters (1 9 13 15 16, 24). From the work by Eddleman et al (7) it seems that elevated values of  $PEP/LVET$  exceeding 0.440 almost always denote decreased LV ejection fraction to be less than 50 %.

In this study we found a weak but statistically significant correlation between the noninvasively determined LV function, as expressed by STI variables, and possible quantitative ECG markers of myocardial necrosis  $\Sigma R$ ,  $\Sigma Q$  and  $\Sigma ST$ . We recognize that STI measurements describing LV function are very indirect and that the correlation with the ECG variables is still far from being a direct expression of LV function, but our findings support the use of  $\Sigma R$  and Q index as indicators of LV performance, as found by others (2 4) except that the  $\Sigma Q$  in our study was the poorest marker.

The use in this study of compound ECG indices (see Table II) did not improve the correlation with the STI variables, but served as an indicator separating the NYHA class 1-2 from the class 3-4 patients, thus confirming a relation between quantitative ECG variables and clinical markers of the severity of myocardial damage.

The correlation between the  $\Sigma ST$ ,  $\Sigma R$  and the various STI variables in anterior MI indicates that, although not a perfect quantitative relation, the standard ECG is a clinically useful indicator of myocardial damage.

# Rocket immunoelectrophoresis of myoglobin in urine in patients with myocardial infarction

K Kølendorf F Pedersen E Christiansen and I Gad

Dept. of Medicine B and Department of Clinical Chemistry  
Kommunehospitalet, COPENHAGEN DENMARK

## Abstract

A rocket immunoelectrophoretic method with prepared antisera to rabbit myoglobin has been developed to study the urinary myoglobin excretion in patients with acute myocardial infarction. The method is able to detect minimum urinary myoglobin concentrations of 1–2 mg/l. Urine specimens from 156 patients admitted to the coronary care unit with a provisional diagnosis of acute myocardial infarction were analysed. Seventy-six patients proved to have documented myocardial infarction. Twelve of them had at least one positive determination. Four of the 80 without infarction had myoglobinuria, 15 hours elapsed from the time of the initial event of chest pain to the first positive urine specimen. No statistically significant difference could be demonstrated in the mortality in patients with infarction with and without myoglobinuria.

The present authors were unable to confirm the high incidence of myoglobinuria in acute myocardial infarction, described previously in other works. The possibility of renal tubular reabsorption of myoglobin as an explanation of this discrepancy is mentioned. Our preliminary results with the estimate of myoglobin in serum with a radioimmunoassay seem to be valuable as an index of infarct size.

Acute myocardial infarction (AMI) is generally diagnosed on the basis of a cha-

racteristic clinical history and typical electrocardiographic and serum enzyme findings. In patients with recent chest pain, and an old infarct pattern, or bundle branch block, these data are insufficient to establish the diagnosis definitely. Therefore efforts have been made to find more sensitive and possibly more specific tests, which might aid in documenting the presence and extent of myocardial necrosis. Damage to the cardiac muscle mass results in release to the circulation of myoglobin, a low molecular weight, oxygen binding heme protein, which is found in and synthesized by cardiac and skeletal muscle (4). Present methods fail to detect the presence of myoglobin in the circulation or the urine. Several investigators have reported that some patients with AMI develop myoglobinemia and myoglobinuria (mgU) which have been detected immunologically (2, 4, 14).

We have developed a rocket immunoelectrophoretic method for detecting myoglobin in urine to evaluate the frequency of mgU in patients with AMI.

## Material and method

### Patients

We studied 156 consecutive patients with a diagnosis of possible AMI admitted to the coronary care unit during an 8-month period. Urine samples were collected from each patient in the first three days, beginning on day of admission. The average time from the onset of chest pain to admission was 16 hours.

- bein, M. C. & Maroko P. R. Use of changes in the epicardial QRS complex to assess interventions which modify the extent of myocardial necrosis following coronary artery occlusion. *Circulation* 54 591 1976
- 12 Karlsson, J. Templeton, G. H. & Wilkerson, J. T. Relationships between S-T segment changes and myocardial metabolism during acute coronary insufficiency. *Circ. Res.* 32 725 1973
- 13 Lewis, R. P., Boudoulas, H., Welch, T. G. & Forester W. F. Usefulness of systolic time intervals in coronary artery disease. *Amer J Cardiol.* 37 787 1976
- 14 Mathey D. Bleifeld W., Hanrath, P. & Effert, S. Attempt to quantitate relation between cardiac function and infarct size in acute myocardial infarction. *Brit. Heart J* 36 271 1974
- 15 McConahay D. R., Carroll, M. M. & Chestlin, M. D. Resting and exercise time intervals. Correlations with ventricular performance in patients with coronary disease. *Circulation* 45 592 1972
- 16 Meng, R. Hollander C., Liebson P. R., Teran, J. C., Barresi, V. & Lunc, M. The use of noninvasive methods in the evaluation of left ventricular performance in coronary artery disease. *Amer Heart J* 90 134 1975
- 17 Miller R. R., Bonanno, J., Massumi, R. A., Zelis, R. F., Mason D. T. & Amsterdam, E. A. Usefulness of the electrocardiogram in assessment of ventricular performance and comparison with coronary arteriography. *Amer J Cardiol* 29 281 1972
- 18 Miller R. R., Amsterdam, E. A. Borgen, H. G. Massumi, R. A. Zelis, R. & Mason, D. T. Electrocardiographic and cineangiographic correlations in assessment of the location, nature and extent of abnormal left ventricular segmental contraction in coronary artery disease. *Circulation* 49 447 1974
- 19 Norris, R. M., Barrat Boyes, C., Heng M. K. & Singh, B. N. Failure of ST segment elevation to predict severity of acute myocardial infarction. *Brit. Heart J* 38 85 1976
- 20 Page, D. L., Caulfield, J. B., Hastor J. A. DeSanctis, R. W. & Sanders, C. A. Myocardial changes associated with cardiogenic shock. *New Engl. J. Med* 285 133 1971
- 21 Radvany P., Askenazi J., Maroko, P. R. & Braunwald, E. Predictive value of ST segment in the development of electrocardiographic signs of necrosis after experimental coronary occlusion. *Circulation* 51 & 52, suppl II 6, 1975
- 22 Scheuer J. & Brachfeld, N. Coronary insufficiency. Relations between hemodynamic, electrical and biochemical parameters. *Circ. Res.* 18 178 1966
- 23 Smith, H. J. Singh, B. N. Norris, R. M. Murray J. B. & Hurley P. J. Changes in myocardial blood flow and S-T segment elevation following coronary occlusion in dogs. *Circ. Res.* 36 697 1975
- 24 Stack, R. S., Lee, C. C., Reddy B. P. Taylor M. L. & Weissler A. M. Left ventricular performance in coronary artery disease evaluated with systolic time intervals and echocardiography. *Amer J Cardiol* 37 331 1976
- 25 Swan, H. J. C. Functional basis of the hemodynamic spectrum associated with myocardial infarction. In *Shock in myocardial infarction*. Eds. Gunnar R. M. Loeb, H. S. & Shabuddin H. R. pp 47-63 Grune & Stratton, New York 1974
- 26 Swartz, M. H. Pritchard, A. D. Meller J. Teichholz, L. E. & Herman, M. V. The normal electrocardiogram as a predictor of left ventricular function in patients with coronary artery disease. *Brit. Heart J* 39 208 1977
- 27 Williams, R. A., Cohn, P. F. Vokonas, P. S. Young E., Herman M. V. & Gorlin, R. Electrocardiographic, arteriographic and ventriculographic correlations in transmural myocardial infarction. *Amer J Cardiol.* 31: 595 1973

# Rocket immunoelectrophoresis of myoglobin in urine in patients with myocardial infarction

K Kølendorf F Pedersen E Christiansen and  
I Gad

Dept. of Medicine B and Department of Clinical Chemistry  
Kommunehospitalet, COPENHAGEN DENMARK

## Abstract

A rocket immunoelectrophoretic method with prepared antisera to rabbit myoglobin has been developed to study the urinary myoglobin excretion in patients with acute myocardial infarction. The method is able to detect a minimum urinary myoglobin concentration of 1–2 mg/l. Urine specimens from 156 patients admitted to the coronary care unit with provisional diagnosis of acute myocardial infarction were analysed. Seventy-six patients proved to have documented myocardial infarction. Twelve of them had at least one positive determination. Four of the 80 without infarction had myoglobinuria. 15 hours elapsed from the time of the initial event of chest pain to the first positive urine specimen. No statistically significant difference could be demonstrated in the mortality in patients with infarction with and without myoglobinuria.

The present authors were unable to confirm the high incidence of myoglobinuria in acute myocardial infarction, described previously in other works. The possibility of renal tubular reabsorption of myoglobin as an explanation of this discrepancy is mentioned. Our preliminary results with the excretion of myoglobin in serum with radioimmunoassay seem to be valuable as an index of infarct size.

Acute myocardial infarction (AMI) is generally diagnosed on the basis of cha-

racteristic clinical history and typical electrocardiographic and serum enzyme findings. In patients with recent chest pain, and an old infarct pattern, or bundle branch block, these data are insufficient to establish the diagnosis definitely. Therefore efforts have been made to find more sensitive and possibly more specific tests, which might aid in documenting the presence and extent of myocardial necrosis. Damage to the cardiac muscle mass results in release to the circulation of myoglobin, a low molecular weight, oxygen binding heme protein, which is found in and synthesized by cardiac and skeletal muscle (4). Present methods fail to detect the presence of myoglobin in the circulation or the urine. Several investigators have reported that some patients with AMI develop myoglobinemia and myoglobinuria (myo) which have been detected immunologically (2, 6, 14).

We have developed a rocket immunoelectrophoretic method for detecting myoglobin in urine to evaluate the frequency of myo in patients with AMI.

## Material and method

### Patients

We studied 156 consecutive patients with a diagnosis of possible AMI admitted to the coronary care unit during an 8-month period. Urine samples were collected from each patient in the first three days, beginning on day of admission. The average time for the onset of chest pain to admission was 16 hours.



### Diagnostic criteria

A standard 9 lead electrocardiogram was performed daily on each patient for 3 consecutive days and analysed for definite myocardial infarction or no infarction according to the criteria of Kjøller (8). Venous blood was taken daily for the first 3 to 5 days for estimating serum glutamicoxaloacetic transaminase, serum lactic dehydrogenase and serum creatine. Seventy-six patients were found to have definite AMI. Eighty patients failed to fulfil the diagnostic criteria. They constituted the control group. The mean age of the infarction group was 65.0 years (44–84) and of the control group 63.8 years (22–83).

### Preparation of myoglobin

Myoglobin isolated from human skeletal muscles obtained at operation, was prepared according to Luginbuhl (11) and further purified by gel filtration on columns of G-100 and G-25 Sephadex. The purified myoglobin eluate was freeze-dried.

### Immunization of rabbits

Antisera to human heart myoglobin were kindly supplied by Bengt W. Johansson, Heart section, General hospital, Malmö, Sweden.

### Rocket immunoelectrophoretic procedure

Rocket immunoelectrophoresis *s.m.* Laurell (9) involved the following techniques: 0.075

M barbital buffer (pH 8.6) was employed in the electrode vessels. To 100 ml of 0.1 M glycine-saline buffer (pH 8.2) was added 1 gm of agarose A 37 and 6 gm of polyethylene glycol 4000. Ten ml of this mixture and 300  $\mu$ l antihuman myoglobin were added to the immunoplates (100–100 mm). Wells, each 2.5 mm in diameter, were then punched into the agar. With the purified myoglobin as a standard 3  $\mu$ l of undiluted urine was added to the plates. The electrophoresis was continued for 2 hours with a stabilized current of 50–60 mA (140–200 V on the power supply). The plates were rinsed in saline 154 M for 2.5 minutes and dried for 30 minutes at about 25°C and finally in a thermostat at 60°C. The quantitation of myoglobin in the samples and in the standard solutions (2, 5, 5, 10 and 20 mg myoglobin/l) were based on comparison of the immunoprecipitates from the upper edge of the application well to the top of the peak. The sensitivity of the method is 1–2 mg myoglobin/l urine. Addition of myoglobin concentrations from 2–20 mg/l urine has shown recovery from 85–110%.

### Urine samples analysed

Urine was collected for each six-hour period for 3 days, and potassium hydrogencarbonate (800 mg/100 ml urine) was instantly added (pH 8.0–8.5) to prevent destroying the myoglobin content. The urine samples were stored at –20°C until study.

Table 1 Number of patients with acute myocardial infarction related to the presence of myoglobinuria and to the time from the initial event of chest pain. The mortality in patients with and without myoglobinuria is shown.

Hours from acute event	No. of patients with positive tests.	No. of patients with negative tests.
0–6	3	15
6–12	2	28
12–24	4	13
> 24	3	8
	12	64
Mortality	4 (33%)	8 (16%)

## Results

Twelve patients with AMI had mgu (16 %) The mortality was 33 % among infarct patients with mgu, and 16 % among patients without mgu, similar to the total material (Table I) These differences are statistically insignificant ( $p > 0.05$ ) None of the patients with mgu had previous muscle trauma. DC was not undertaken. No correlation was found between the time from initial event of chest pain and the frequency of mgu

(Table I) Most of the 80 patients without AMI suffered from ischaemic heart disease (IHD) 10 had chronic bronchitis, pulmonary embolism or pulmonary neoplasm (Table II) The test for myoglobin was positive in 4 of which 3 had IHD and 1 pulmonary neoplasm (Table II) In 10 patients with AMI serum-creatinine was raised ( $> 1.5$  mg/100 ml) Five of them had mgu (mean se-creatinine 3.9 Mean se-creatinine was 2.4 mg/100 ml in the other 5 patients (Table III)

Table II The final diagnosis in 80 patients without myocardial infarction. Three patients had more than one diagnosis

Diagnosis	No.	No. with positive tests
Ischaemic heart disease	57	3
Myocarditis	1	
Exacerbation in chronic bronchitis	6	
Pneumonia	2	
Pulmonary embolism, pulmonary neoplasm	3	1
Duodenal ulcer (X-ray verified)	2	
Calculus	2	
Other	10	

Table III Serum-creatinine value in 10 patients with acute myocardial infarction and chronic renal failure related to the presence of myoglobinuria

	Serum-creatinine values (mg/100 ml)				
AMI + mgu	3.3	1.8	3.9	7.8	4.9
AMI - mgu	1.8	1.9	2.0	2.4	3.8

### Diagnostic criteria

A standard 9-lead electrocardiogram was performed daily on each patient for 3 consecutive days and analysed for definite myocardial infarction or no infarction, according to the criteria of Kjeller (8). Venous blood was taken daily for the first 3 to 5 days for estimating serum glutamicoxaloacetic transaminase, serum lactic dehydrogenase, and serum creatine. Seventy-two patients were found to have definite AMI. Eighty patients failed to fulfil the diagnostic criteria. They constituted the control group. The mean age of the infarction group was 65.0 years (44–84) and of the control group 63.8 years (22–83).

### Preparation of myoglobin

Myoglobin isolated from human skeletal muscles obtained at operation was prepared according to Luginbuhl (11) and further purified by gel filtration on columns of G-100 and G-25 Sephadex. The purified myoglobin eluate was freeze-dried.

### Immunization of rabbits

Antisera to human heart myoglobin were kindly supplied by Bengt W. Johansson, Heart section, General hospital Malmö, Sweden.

### Rocket immunoelectrophoretic procedure

Rocket immunoelectrophoresis *à la* Laurell (9) involved the following techniques: 0.075

M barbital buffer (pH 8.6) was employed in the electrode vessels. To 100 ml of 0.1 M glycine-saline buffer (pH 8.2) was added 1 gm of agarose A 37 and 6 gm of polyethylene glycol 4000. Ten ml of this mixture and 300  $\mu$ l antihuman myoglobin were added to the immunoplates (100–100 mm). Wells, each 2.5 mm in diameter were then punched into the agar. With the purified myoglobin as a standard, 3  $\mu$ l of undiluted urine was added to the plates. The electrophoresis was continued for 2 hours with a stabilized current of 50–60 mA (140–200 V on the power supply). The plates were rinsed in saline 154 M for 2.5 minutes and dried for 30 minutes at about 25 °C and finally in a thermostat at 60 °C. The quantitation of myoglobin in the samples and in the standard solutions (2, 5, 5, 10 and 20 mg myoglobin/l) were based on comparison of the immunoprecipitates from the upper edge of the application well to the top of the peak. The sensitivity of the method is 1–2 mg myoglobin/l urine. Addition of myoglobin concentrations from 2–20 mg/l urine has shown recovery from 85–110 %.

### Urine samples analysed

Urine was collected for each six-hour period for 3 days, and potassium hydrogencarbonate (800 mg/100 ml urine) was instantly added (pH 8.0–8.5) to prevent destroying the myoglobin content. The urine samples were stored at  $\pm 20^{\circ}\text{C}$  until study.

*Table 1* Number of patients with acute myocardial infarction related to the presence of myoglobinuria and to the time from the initial event of chest pain. The mortality in patients with and without myoglobinuria is shown.

Hours from acute event	No. of patients with positive tests	No. of patients with negative tests
0–6	3	15
6–12	2	28
12–24	4	13
> 24	3	8
	12	64
Mortality	4 (33 %)	8 (16 %)

10. Levine, R. S., Alterman, M., Gubner R. S. and Adams Jr. E. C. Myoglobinaemia in myocardial infarction. *Am J Med Sci* 262: 179 1971
11. Lugnbuhl, W. H.: A method of crystallization of human myoglobin. *Proc Soc Exper Biol and Med* 105 504 1960.
12. Maack, T.: Renal Handling of low molecular weight proteins. *Amer J Med* 58 57 1975
13. Saranchak, H. J. and Bernstein, S. H. A new diagnostic test for acute myocardial infarction. *JAMA* 228 1251 1974
14. Stone, M. J. Willerson, J. T. Gomez Sanchez C. E. and Watterman, M. R. Radioimmunoassay of myoglobin in human serum. *J Clin Invest* 56 1334 1975.

## Discussion

Myoglobinuria after myocardial infarction has been assayed by various immunological techniques. Adams and Elliott (1) tested urine by haemagglutination inhibition assay and found myoglobinuria in 34 of 44 patients with myocardial infarction, and in 16 with out obvious cardiac muscle disease. Levine and co-workers (10) using the same technique found mgu in 34 of 37 patients after myocardial infarction. Only 1 of 28 patients with other cardiopulmonary diagnosis had myoglobinuria. Saranchak and Bernstein (13) with radial immunodiffusion technique found mgu in 59 of 60 patients and none in the control group. Kagen and co-workers (6) demonstrated mgu in 3 of 7 patients with AMI. By means of a complementfixation test, the authors found no correlation between myoglobinemia or myoglobinuria. Kessler and co-workers (7) found myoglobinuria in 15 of 24 patients. None in the control group had mgu. Donald and co-workers (3) using a haemagglutination inhibition method, found that 14 of 16 patients with definite myocardial infarct had mgu. None of the 17 patients with possible infarct had mgu.

We found mgu in 12 of 76 patients with definite myocardial infarction (16%) and in 4 of 80 patients without infarction.

Studies on the renal handling of low molecular weight proteins (especially lysozyme) (12) show that these are filtered freely through the glomerulus membrane. In the proximal tubular cells, these proteins are resorbed and released to the circulation either as intact molecules or as catabolic products. The occurrence of myoglobin in the urine therefore will depend on the amount of filtered myoglobin. The exact renal threshold for myoglobin is obscure but based on animal experiments, a value of 10–20 mg/100 ml serum seems reasonable (5).

Studies in serum from AMI patients (14) show that the myoglobin concentration in serum seldom exceeds 1 mg/100 ml. These findings reasonably explain the few positive results in our studies. In patients with disturbed tubular function, a loss of low mole-

cular weight proteins via urine have been demonstrated. In accordance with this, 5 of 10 patients in the present study with raised se-creatinine and AMI had mgu.

We conclude that detection of myoglobinuria is ineffective as a diagnostic method for AMI probably due to a tubular resorption of myoglobin. However our preliminary results with estimates of myoglobin in serum seem to be valuable as an index of infarct size.

## References

- 1 Adams J., E. C. and Elliott, T. A. Urinary myoglobin in myocardial infarction. *JAMA* 211 1013 1970
- 2 Bernstein, S. H. Myoglobinuria and myocardial infarction. *JAMA* 231 138 1975
- 3 Donald, T. G., Glooman, M. J. Neale Cynthia and Wilchen, D. E. L. Excretion of myoglobin in urine after acute myocardial infarction. *Br Heart J* 39 29 1977
- 4 Kagen, L. J., Lawrence, J. and Christian, C. L. Immunologic measurements of myoglobin in human adult and fetal skeletal muscle. *Am J Physiol* 211 656, 1966
- 5 Kagen L. J. Myoglobinemia and myoglobinuria in patients with myositis. *Arthritis and Rheumatism* 14 457 1971
- 6 Kagen, L. J., Scheidt, S. Roberts L., Porter A. and Paul, H. Myoglobinemia following acute myocardial infarction. *Am J Med* 58 177 1975
- 7 Kessler H. A., Liebson, P. R. Martenheimer H. and Adams Jr. E. C. Acute myocardial infarction diagnosed by myoglobinuria. *Arch Intern Med* 135 1181 1975
- 8 Kjoller E. The long term prognosis after acute myocardial infarction. *Dan Med Bull* 22 202 1975
- 9 Laurell C. B. Electroimmuno assay. *Scand J Clin Lab Invest* 29 suppl 124 21 1972.

10. Levine, R. S. Alterman, M., Gubner R. S. and Adams J. E. C. Myoglobinuria in myocardial infarction. *Am J Med Sci* 262: 179 1971
11. Laggobuhl, W. H. A method of crystallization of human myoglobin. *Proc Soc Exper Biol and Med* 105: 504 1960
12. Maack, T. Renal Handling of low molecular weight proteins. *Amer J Med* 58: 57 1975
13. Sarachak, H. J. and Bernstein, S. H. A new diagnostic test for acute myocardial infarction. *JAMA* 228: 1251 1974
14. Stone, M. J. Willerson, J. T. Gomez Sanchez, C. E. and Wauterman, M. R.: Radioimmunoassay of myoglobin in human serum. *J Clin Invest* 56: 1334 1975

## PANEL DISCUSSION

Bengt W. Johansson A diagnosis of acute myocardial infarction is often easy to verify. In many instances, however, the common diagnostic armamentarium is not enough and a clearcut diagnosis cannot be given. This is so especially in patients who on admission have ECG changes due to a previous infarction, bundle branch block or intraventricular conduction disturbances, and in patients with a long time interval between onset of symptoms and admission to hospital. Furthermore, uncharacteristic symptoms or multiple attacks of chest pain in many patients will make it impossible to decide precisely when the infarction started. An enzyme peak might have occurred before admission to the hospital.

To obviate these difficulties, new aids to diagnose an acute myocardial infarction have

been developed. Those most often discussed in living patients during recent years are ST mapping, specific cardiac isoenzymes, radio-nuclides, and myoglobin in urine or serum.

The early statement that CK MB is a cardiospecific isoenzyme has been questioned, and recent reports have claimed that a certain percentage of CK MB is found in tissues other than cardiac, including skeletal muscle. This might be of importance in patients with an impaired peripheral circulation due to an acute infarction. As the amount of skeletal muscle is much greater than the amount of cardiac muscle even a small leakage of CK MB from skeletal muscle will influence the serum values. Moreover there are technical difficulties that, from a clinical point of view might be of minor importance.

### Some pitfalls in the determination of S creatine kinase B-subunit activity with an immunoinhibition method

L. Ljungdahl, W. Gerhardt and S. Hofvander

Dept. of Clinical chemistry and Dept. of Medicine,  
The hospital of Helsingborg HELSINGBORG SWEDEN

We recently described an immunoinhibition method for routine determination of S-CK B subunit activity (1, 2). This method is based on the SCE recommended S-CK method  $\pm$  antibody (3). Completeness and specificity of the immunoinhibition were achieved by the earlier described titration experiments with anti M (1).

In contrast to existing commercially available, one step S-CK MB procedures, our method comprises correction for individual adenylate kinase (EC 2.7.4.3 AK) sample blank activities, correction for the very small residual fraction of non-inhibited CK MM activity and correlation of S-CK B results to total S-CK activity. The method has for more than a year been in routine use on the

LKB 8600 reaction rate analyzer in our laboratory.

We make 3 separate measurements on each sample:

- 1) S-CK B in the presence of anti M
- 2) Total S-CK
- 3) S-AK activity

Previous studies have shown that the immunoinhibition of CK MM is 99.0–99.7 per cent complete. However, with the AMI discrimination limit for S-CK B set at 15 U/l (2) even 1 per cent of a total S-CK activity of 1500 U/l in a non AMI patient would appear as a false positive S-CK B result. In order to avoid any contribution of residual non inhibited CK MM activity an arbitrary 1 per cent of the total S-CK acti-

ROUTINE DISCRIMINATION OF CK-B ACTIVITY IN SERUM SIZE CK METHOD    AMI-N		
CK REAGENT	ENZYME ACTIVITIES MEASURED	CALCULATION
+ANTI-B	CK B CK M or CK MB AK	APPARENT CK B
-ANTI-B	TOTAL CK CK M CK MB CK MB CK MB	CK M TOTAL CK
-ANTI-B -CREATINE PHOSPHATE	MUSCLE AK Erythrocytes Thrombocytes Liver Muscle	AK
		CK B

Fig. 1

Table I Cumulative frequency distribution of 1367 S-AK blank sites measured in the SCE CK reagent without creatine phosphate

N	U/l	Per cent
909	0—3.7	37.2
707	0—7.4	88.9
102	0—11.1	96.4
29	0—14.8	98.5
20	>14.8	100.0

has been carried out in all S-CK B determinations.

An evaluation of 288 non AMI patients showed that, with the used discrimination limit of 15 U/l (2) for S-CK B activity 56 false positives (19 per cent) were voided by this correction (Table II).

Examples are given below that demonstrate the specificity of the S-CK B determinations achieved by the described corrections.

The first example (Fig. 2) is where S-CK B activity constituted less than 0.5 per cent of a highly increased total S-CK activity. A 73 year old man was admitted to the CCU with suspected acute myocardial infarction. For one to two weeks before admission, he had suffered attacks of chest pain suggestive of angina pectoris. Serum enzyme determina-

tion was consequently subtracted from the directly measured S-CK B activity (Fig. 1).

One of the main problems in the determination of S-CK B activity is the interference by AK (4, 5, 6). AK activity in serum originates from several sources including erythrocytes, thrombocytes, liver and muscle tissue (4, 5, 6). One of the innovations in the SCE CK reagent was the combination of two AK inhibitors, ADP and P<sub>i</sub> P<sub>i</sub>-di adenosine 5-pentaphosphate. A detailed description has been given of the efficiency and specificity of the inhibitor combination (4, 5, 6).

It inhibits 99 % AK from erythrocytes and muscle and about 90 % from liver. However, residual AK activity is measurable and can to a greater or lesser degree contribute to a falsely increased, apparent S-CK B activity. Table I shows cumulative frequency distribution of 1367 AK sample blanks from AMI and non-AMI patients. As our routine procedure incorporates a determination of individual sample AK blank activity a correction for this interference

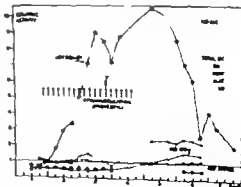


Fig. 2.



Table II Frequency of S-AK values that would have caused false positive S-CK B results if S-AK sample blanks had not been subtracted

	Number of patients	Samples
Non AMI patients, total	288	1055
Non AMI patients in which subtraction of individual S-AK (sample blanks) <sup>1</sup> reduced increased S-CK B values to <15 U/l	56 (19.4%)	77 (7.3%)

1 after subtraction of 1% of total S-CK from apparent S-CK B

tions were made on admission and subsequently at six hour intervals.

The horizontal line at 1 on the ordinate represents the upper reference limit for each enzyme except for S-CK B where the line represents the discrimination value. (Ch MB=0) and (LD 150) designate the time when isoenzyme electrophoreses were performed. The initial values of S-aspartate aminotransferase (S-ASAT) S-alanine aminotransferase (S-ALAT) total S-CK and S-CK B activities were within the reference range, whereas S-lactate dehydrogenase (S LD) was slightly above

After admission, the patient developed a ventricular arrhythmia. This was treated with intramuscular injections of procaine amide (Procrystil®) at four hour intervals. Within eight hours after the first injection, total S-CK activity had increased by a factor of 4. It reached peak values of about 1500 U/l to 1700 U/l where it remained during the next four days.

The clinicians diagnosed the condition as non-myocardial infarction. This was supposed on the basis of the patient's history ECG lacking the criteria for AMI and on the routine enzyme analyses then available. The diagnosis agreed fully with the enzyme pattern plotted in Fig 2. In this case, S-CK B would have been well above the discrimination limit of 15 U/l unless subtraction of 1 per cent of total S-CK had been made

Fig. 3 shows the sensitivity of the immunoblotting system. Both cases in this figure showed only relatively moderate elevations of total S-CK activities. The upper panel represents a 67 year old female who suffered intermittent chest pain attacks (arrows in figure) before the rise in serum enzyme activities. S-CK MB and S-LD H<sub>4</sub> isoenzymes were elevated electrophoretically in the samples indicated in the figure. Total S-CK and S-ASAT were increased, thus confirming the diagnosis of AMI (2) S-CK B activity was above the discrimination limit and showed a time course parallel with that of total S-CK. ECG was suggestive of an anterior wall infarction but was not conclusive. The lower panel in Fig 3 represents a 59 year old female who had suffered chest pain

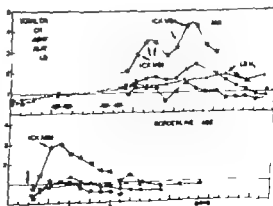


Fig 3

Table III Examples of non-AMI patients in which subtraction of 1% of total S-CK prevents false positive CK B values.

Patient age	Clinical situation	Serum Enzymes (U/l)				
		Total CK	Uncorrected CK B	AK	CK B - AK	CK B - AK - 1% of tot. CK
♂ 67	Biliary occlusion	72	22.8	16.8	6.0	5.4
♂ 45	Chest pain, non AMI	108	15.6	9.6	6.0	4.8
♂ 59	Ventr fibr non AMI	120	18.6	12.0	6.6	5.4
♂ 56	Myalgic pain	138	24.6	16.2	8.4	7.2
♀ 78	Heart failure	144	17.4	10.8	6.6	5.4
♂ 76	Heart failure	192	18.0	6.0	12.0	10.2
♂ 72	Angina pectoris	360	19.2	4.2	15.0	11.4
♀ 75	After orthop surgery	540	21.0	5.4	15.6	10.2
♂ 63	Pulmonary embolism	660	19.2	3.0	16.2	9.6
♂ 39	Repeated I.M. inj	936	25.8	4.2	21.6	12.0
♂ 25	After physio. exercise and possible viral myositis	984	18.6	3.0	15.6	6.0
♂ 56	After orthop surgery	1320	22.2	3.0	19.2	6.0

Table IV

Predictability / S-CK B

	Neg	Pos	
AMI	1	52	53
non AMI	56	0	56
	57	52	Total 109

PV Pos = 1.0  
PV Neg = 0.98

Predictability of total S-CK

	Neg	Pos	
AMI	0	53	53
non AMI	51	5	56
	51	58	Total 109

PV Pos = 0.91  
PV Neg = 1.0

*Table 11 Frequency of S-CK values that would have caused false positive S-CK B results if S-CK sample blanks had not been subtracted*

	Number of patients	Samples
Non AMI patients, total	288	1055
Non AMI patients in which subtraction of individual S-CK (sample blanks) reduced increased S-CK B values to <15 U/l	56 (19.4%)	77 (7.3%)

1 after subtraction of 1% of total S-CK from apparent S-CK B

utions were made on admission and subsequently at six hour intervals.

The horizontal line at 1 on the ordinate represents the upper reference limit for each enzyme except for S-CK B where the line represents the discrimination value. (CK MB=0) and (LD iso) designate the time when isoenzyme electrophoreses were performed. The initial values of S-aspartate aminotransferase (S-ASAT) S-alanine aminotransferase (S-ALAT) total S-CK and S-CK B activities were within the reference range, whereas S-lactate dehydrogenase (S-LD) was slightly above.

After admission, the patient developed a ventricular arrhythmia. This was treated with intramuscular injections of procaine amide (Pronestyl®) at four-hour intervals. Within eight hours after the first injection total S-CK activity had increased by a factor of 4. It reached peak values of about 1500 U/l to 1700 U/l where it remained during the next four days.

The clinicians diagnosed the condition as non myocardial infarction. This was supposed on the basis of the patient's history ECG lacking the criteria for AMI and on the routine enzyme analyses then available. The diagnosis agreed fully with the enzyme pattern plotted in Fig. 2. In this case, S-CK B would have been well above the discrimination limit of 15 U/l unless subtraction of 1 per cent of total S-CK had been made.

Fig. 3 shows the sensitivity of the immunodiffusion system. Both cases in this figure showed only relatively moderate elevations of total S-CK activities. The upper panel represents a 67 year old female who suffered intermittent chest pain attacks (arrows in figure) before the rise in serum enzyme activities. S-CK MB and S-LD H<sub>4</sub> isoenzymes were elevated electrophoretically in the samples indicated in the figure. Total S-CK and S-ASAT were increased, thus confirming the diagnosis of AMI (2). S-CK B activity was above the discrimination limit and showed a time course parallel with that of total S-CK. ECG was suggestive of an anterior wall infarction but was not conclusive. The lower panel in Fig 3 represents a 59 year old female who had suffered chest pain

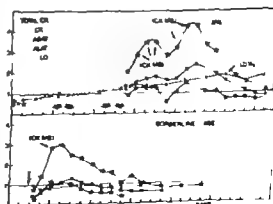


Fig 3

Table III Examples of non-AMI patients in which subtraction of 1% of total S-CK prevents false positive CK B values

Patient age sex	Clinical situation	Serum Enzymes (U/l)				
		Total CK	Uncorrected CK B	AK	CK B — AK	CK B — AK — 1% of tot. CK
♂ 67	Biliary occlusion	72	22.8	16.8	6.0	5.4
♂ 45	Chest pain, non AMI	108	15.6	9.6	6.0	4.8
♂ 59	Ventr fibr non AMI	120	18.6	12.0	6.6	5.4
♂ 56	Myalgic pain	138	24.6	16.2	8.4	7.2
♀ 78	Heart failure	144	17.4	10.8	6.6	5.4
♂ 76	Heart failure	192	18.0	6.0	12.0	10.2
♂ 72	Angina pectoris	360	19.2	4.2	15.0	11.4
♀ 75	After orthop surgery	540	21.0	5.4	15.6	10.2
♂ 63	Pulmonary embolism	660	19.2	3.0	16.2	9.6
♂ 39	Repeated L.M. inj.	936	25.8	4.2	21.6	12.0
♂ 25	After physc. exercise and possible viral myositis	984	18.6	3.0	15.6	6.0
♂ 56	After orthop surgery	1320	22.2	3.0	19.2	6.0

Table IV

Predictability / S-CK B

	Neg	Pos	
AMI	1	52	53
non AMI	56	0	56
	57	52	Total 109

PV Pos = 1.0  
PV Neg = 0.98

Predictability of total S-CK

	Neg	Pos.	
AMI	0	53	53
non AMI	51	5	56
	51	58	Total 109

PV Pos = 0.91  
PV Neg = 1.0

for 3 hours before admission (arrow). The activities of total S-CK, S-CK II and S-ASAT were only slightly increased. S-LD H<sub>4</sub> was not increased. On the other hand, S-CK MB was twice detected on electrophoresis. ECG indicated the possibility of a sub-endocardial infarction but was not conclusive. On the basis of these data, this was considered a borderline case (2).

Table III summarizes a number of non-AMI cases in which subtraction of either S-AK activity measured in the individual samples or 1 per cent of total S-CK activity prevents false positive S-CK II values.

Determination of total S-CK in the diagnosis of acute myocardial infarction has the disadvantage of a low clinical specificity (2). Determination of CK isoenzymes considerably increases the specificity. When using an immunoinhibition technique for CK isoenzyme analysis, the two above-described pitfalls must be taken into account to retain the clinical specificity. Practically a flexible NAC activated CK reagent system including anti M is now under development by E. Merck.

The problem of clinical specificity cannot be solved by simply elevating the discrimination limit. This would inevitably lead to a decrease in the clinical sensitivity.

With serial determinations performed on samples taken at 6-hour intervals, as indicated in Figs. 2 and 3 the diagnostic value of total S-CK and S-CK B was evaluated (2). This was done on a patient material comprising 109 non-AMI and AMI cases with an AMI prevalence of 0.49. Table IV shows the obtained predictive values of total S-CK and S-CK B.

## Acknowledgement

Grants from the Thorsten and Elsa Seger Falks Foundation, Helsingborg, Sweden supported the investigation.

## References

- 1 Gerhardt, W., Ljungdahl, L., Hofvendahl, S., Björjesson, J., & Hedenäs, B. Creatine kinase B-subunit activity in human serum I Development of an immunoinhibition method for routine determination of S-Creatine kinase B-subunit activity. *Clin Chim Acta* 78: 29, 1977.
- 2 Ljungdahl, L., Hofvendahl, S., Gerhardt, W., & Björjesson, J. Creatine kinase B-subunit activity in human serum II Evaluation of S-CK B-subunit activity in the diagnosis of acute myocardial infarction. *Clin Chim Acta* 78: 43, 1977.
- 3 The Committee on Enzymes of the Scandinavian Society for Clinical Chemistry and Clinical Physiology Recommended Method for the Determination of Creatine Kinase in Blood. *Scand J Lab Invest.* Vol 36, 1976.
- 4 Szasz, G., Gruber, W., Berni, E. Creatine Kinase in serum 1 Determination of optimum reaction conditions. *Clin Chem* 22: 650, 1976.
- 5 Szasz, G., Gerhardt, W., Gruber, W., Berni, E. Creatine Kinase in Serum 2 Interference of Adenylate Kinase with the Assay. *Clin Chem* 22: 1806, 1976.
- 6 Szasz, G., Gerhardt, W., Gruber, W. Creatine Kinase in Serum 3 Complementary Study of Adenylate Kinase Inhibitors. *Clin Chem*, in press.

*Added in proof:* Subsequent experiments after this report was written documented that it is unnecessary to determine S-CK B if total S-CK is below the discrimination limit for AMI. Investigations of newer batches of anti M (1978) have shown that the immunoinhibition of isoenzyme MM is so close to 100% that the subtraction of 1% of total S-CK is unnecessary.

Bengt W. Johansson. The isoenzymes most often discussed in the literature is CK MB. But LD isoenzymes are of great help in patients hospitalized late after symptoms and in order to differentiate between an LD

elevation due to myocardial damage and hepatic leakage secondary to a cardiac decompensation. In addition, ASAT isoenzymes might be of value.

## Accurate determination of serum ASAT isoenzymes

Aarne Kontunen and Kaarina Ojala

Kivela Municipal hospital, HELSINKI FINLAND

### Abstract

An improved electrophoretic modification for measuring aspartate aminotransferase (ASAT) isoenzymes is presented. This method fulfils the clinical requirements for sensitivity and allows the detection of 1 U/l mitochondria ASAT activity at 25°C. The procedure is relatively simple, requiring about one hour for series of 8 determinations. Mitochondrial ASAT activity was found in all patients suffering from acute myocardial infarction pathological activity was observed for several days longer than that of total serum ASAT enzyme. None of the 25 healthy people studied had mitochondrial ASAT in their serum.

Efforts have been made to use the activity of aspartate aminotransferase (ASAT) isoenzymes to confirm acute myocardial infarction. ASAT consists of two isoenzymes which, in contrast to other isoenzymes, are not specific to certain organs. One is located in the cytoplasm and the other within the mitochondria (1). The release of mitochondrial ASAT isoenzyme into the serum thus indicates the degree of cell damage caused by necrotic injury to the mitochondrial membranes. Of the several procedures proposed for the separation of ASAT isoenzymes, only electrophoresis is applicable in the clinical laboratory.

The earliest electrophoretic method which made feasible the quantitation of the isoenzymes (4, 5) is too insensitive for routine use. Our new modification fulfils the requirements for sensitivity (1 U/l  $\pm$  25%) and is simple enough for day-to-day use. The procedure takes one hour and only routine reagents are needed.

The proposed method is based on an electrophoretic run on commercial cellulose acetate membranes, and the fractions of ASAT are visualized by the colour reaction with Fast Violet B. The Beckman Microzone system with barbital buffer pH 8.6 and ionic strength 0.075 M is used. The stock agar solution is made by melting 2 g agar (Difco Agar Noble) in 50 ml water in boiling bath. The solution is divided into 4 ml fractions. These are stable for 2 weeks at 4°C.

The substrate buffer contains Tris (by diisoxymethyl) aminomethane, 1.2 g, L aspartic acid (Merck) 2.66 g, 2-oxoglutaric acid (Merck) 350 mg, Polyvinylpyrrolidone, 3 g and N EDTA, 460 mg, dissolved in re-distilled water pH adjusted to 7.4 and made up to 100 ml with distilled water. This buffer keeps for one month at 4°C.

The substrate gel is prepared by melting 4 ml of the stock agar solution in boiling water bath, mixing it with 4 ml of substrate buffer and with 0.25 ml of pyridoxalphosphate solution (KABI in tablet form, containing 0.83 mg/tablet) made by dissolving

one tablet in 1 ml of water. After mixing the solution is poured immediately into a Petri dish. Pyridoxalphosphate solution must be prepared immediately before use whereas the substrate gel will keep for several days at 4°C.

A serum volume of 0.25—1.00 µl, depending on the ASAT activity is applied to the cellulose acetate strips with a running time of 20 minutes at 250 V. The membrane is then layered on to the substrate gel and incubated at 37°C for 30 minutes. After incubation, the isoenzymes are coloured as follows: another strip soaked in Fast Violet B (40 mg/1 ml of H<sub>2</sub>O prepared just before use) and blotted slightly is layered on the membrane (which is not removed from the gel) and left for 10 minutes at 37°C. The membrane is fixed by immersing in 5% acetic acid for about two minutes, rinsing in water and drying in air. The scanning is made at 540 nm with a Helena Auto Scanner (Fig. 1).

The mitochondrial ASAT isoenzyme was not detectable in the serum of 25 healthy people studied. This is a useful result as it strongly suggests that the enzyme is present

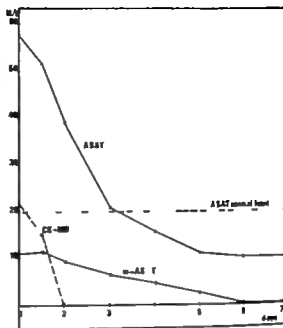


Fig. 2 Daily measurements of total ASAT and mitochondrial (m-ASAT) and MB isoenzyme of creatine kinase (CK-MB) in a patient having had acute myocardial infarction 24 hours earlier.

only in pathological processes in the body. In conformity with these findings, mitochondrial ASAT isoenzyme has not been detectable in healthy subjects by our earlier method or by more complicated and refined techniques (reviewed by Wilkinson) (6). Boyde's (2, 3) results, however, derived with a semiquantitative method suggest that minimum activities of mitochondrial ASAT might be present in normal serum.

We have found serum mitochondrial ASAT isoenzyme to be a very sensitive indicator of acute myocardial infarction. According to our findings, it is a considerably more accurate indicator for the detection of myocardial damage than total ASAT activity. The augmentation of mitochondrial ASAT appears to take place a few hours later but remains detectable for several days longer than total serum ASAT activity (Fig. 2). Thus the determination of mitochondrial ASAT might be used to help confirm an infarct, for instance if the heart-specific isoenzyme of creatine kinase (CK-MB) is suspected of having disappeared from

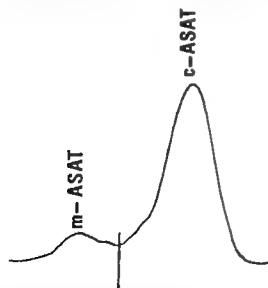


Fig. 1 Representative scanning of ASAT isoenzymes of a patient with acute myocardial infarction. Total serum ASAT 40 U/l, cytoplasmic (c-ASAT) 34 U/l and mitochondrial (m-ASAT) 6 U/l.

the serum. Despite the superior specificity of serum CK-MB isoenzyme in myocardial damage, its use is handicapped by excessively quick disappearance from the serum. The determination of mitochondrial ASAT might be particularly valuable, for instance, where a negative CK-MB finding is suspected of being due to delayed admission.

Because, in addition to the myocardium, mitochondrial ASAT isoenzyme is also present, for instance, in the liver leakage from here into the serum might take place if mitochondrial membranes of cells are damaged sufficiently. An important point in the diagnosis of myocardial infarction is whether liver congestion is superimposed on the infarction, and whether such congestion is severe enough to cause rupture of the double membranes of the mitochondria. According to our earlier method, modest congestion of the liver was not followed by increased mitochondrial ASAT activity in the serum (5). Our initial observations with the present method have not helped to solve this question, although massive liver damage has been observed to lead to the appearance of mitochondrial ASAT isoenzyme in the serum.

In studying highly icteric sera, an additional band is formed on the strip because conjugated bilirubin reacts with the diazonium salt. This band does not move from the application groove and is thus clearly separable from the ASAT isoenzymes. The eventual clinical value of ASAT isoenzyme

determinations is still to be evaluated in further studies, for which the present sensitive and simple method appears to offer fresh possibilities.

## References

1. Boyd, J. W.: The intracellular distribution, latency and electrophoretic mobility of L-glutamate-oxaloacetate transaminase from rat liver. *Biochem. J.* 81:434 1961.
2. Boyde, T. R. C.: Detection and assay of mitochondrial aspartate aminotransferase in serum. *Z. Klin. Chem.* 6:431 1968.
3. Boyde, T. R. C.: Serum levels of the mitochondrial isoenzyme of aspartate aminotransferase in myocardial infarction and muscular dystrophy. *Enzym. Biol. Clin.* 9:385 1968.
4. Murros, J., Kontinen, A., & Somer, H.: An electrophoretic method for the quantitation of aspartate aminotransferase isoenzymes. *Clin. Chim. Acta* 41:263 1972.
5. Murros, J., Kontinen, A., & Somer, H.: Mitochondrial aspartate aminotransferase in myocardial infarction. *Clin. Chim. Acta* 48:241 1973.
6. Wilkinson, J. H.: Chemistry of enzymes of diagnostic interest. In: *T. Principles and Practice of Diagnostic Enzymology* (ed. J. H. Wilkinson) pp. 82-89. Edward Arnold Publ. Ltd., London 1974.

## Creatine kinase isoenzymes in the confirmation of acute myocardial infarction

Aarne Kontinen

Kivela Municipal hospital, HELSINKI FINLAND

### Abstract

Serum MB isoenzyme of creatine kinase is the most specific and sensitive indicator of myocardial infarction. Despite these virtues, its clinical use is handicapped by rapid nor-

malization after the onset of myocardial injury. In patients suffering brain accidents, the increase of serum CK-MB isoenzymes indicates simultaneous myocardial damage and means poor prognosis.



The conventional serum enzyme tests for confirming acute myocardial infarction have their shortcomings. The unspecificity of the tests, especially has been a challenge to the development of better methods. Since the early 1960s, it has been known that, of the three isoenzymes of creatine kinase (CK) the hybrid form (MB) is not found in significant quantities outside the myocardium.

Methodological difficulties, however hampered the clinical use of MB isoenzyme in the detection of myocardial infarct. This obstacle was overcome in 1972, and preliminary findings suggested that CK MB isoenzyme might have clinical significance for confirming acute myocardial infarction (3). Since then keen research work has produced more refined methods, which have demonstrated the superiority of CK MB isoenzyme in the confirmation of acute myocardial infarct. It surpasses the other methods in both specificity and sensitivity (4). The virtue of the CK MB isoenzyme determination has been verified in a large number of studies (see, e.g. 7-8).

Serum CK MB isoenzyme determination is often the only enzyme test that in complicated cases, makes possible the confirmation or exclusion of necrosis in the myocardium. When suspicion of an infarct is aroused, for instance, after operation, in shock, after muscle trauma, coronary angiography or cardiac catheterization, the serum CK MB isoenzyme determination offers the only reliable indicator for verifying myocardial injury.

It is often difficult to differentiate between pulmonary embolism and myocardial infarction. The similarities in the clinical picture — ECG changes mimicking myocardial infarct and elevations in conventional serum enzymes — confuse the matter. Moreover in connection with pulmonary embolism an anginal attack without an infarct — due to diminished coronary blood flow — could cause further diagnostic difficulties. In such situations where there is no myocardial infarction, the CK MB isoenzyme remains normal (5).

The main disadvantage of the clinical use of the CK MB isoenzyme is that its activity normalizes very rapidly after myocardial infarct. This is a particular handicap where the precise time of onset of an infarct is uncertain. Another problem although of minor clinical significance is that muscular dystrophies, such as Duchenne's and Becker's diseases, almost always elevate serum CK MB isoenzyme (10) evidently because of changes in the skeletal muscles (9) although a contribution of heart damage in such patients cannot be excluded. However the characteristic clinical picture, together with muscular studies, makes it easy to distinguish dystrophic patients from those suspected of suffering from myocardial infarction.

The normal serum activity of creatine kinase consists of muscle type (MM) isoenzyme the brain-type (CK BB) has only recently been discovered in the serum (1-6). This was thought not to have any clinical importance, although recent findings have hinted that it might be of diagnostic significance in cerebral accidents (1-11). Cerebral trauma and severe cerebral injuries are accompanied by a release of brain-type (BB) isoenzyme into the serum, but more local brain damage such as ischaemic brain injury elevates serum BB isoenzyme only very occasionally whereas diffuse brain damage is often accompanied by elevation of BB isoenzyme in the serum (1). The final clinical significance of the brain-type CK isoenzyme is still to be established, and the present superficial knowledge requires additional support. Acute brain damage which frequently appears superimposed by myocardial damage as indicated by ECG serum CK MB, and autopsy worsens prognosis significantly with or without serum BB elevations (2).

## References

1. Kaste, M., Somer H & Kontinen A. Brain type creatine kinase isoenzyme. *Arch. Neurol* 34 142, 1977.
2. Kaste, M. Somer H & Kontinen A. Heart type creatine kinase isoenzyme (CK MB) in acute cerebral disorders. *Brit. Heart J* 40 802 1978.

- 3 Kontinen, A. & Somer H.: Determination of serum creatine kinase isoenzymes in myocardial infarction. *Amer J Cardiol* 29: 817 1972.
- 4 Kontinen, A. & Somer H.: Specificity of serum creatine kinase isoenzymes in diagnosis of acute myocardial infarction. *Brit. med. J.* 1 386, 1973
- 5 Kontinen, A., Somer H. & Auvinen, S.: Serum enzymes and isoenzymes. Extrapulmonary sources in acute pulmonary embolism. *Arch. intern. Med.* 133: 243 1974
- 6 Nelson, D. A. & Henderson, A. R.: Measurement of brain-specific creatine kinase isoenzyme activity in serum. *Clin. Chem.* 21 1663 1975
- 7 Roberts, R. & Sobel, B. E.: Elevated plasma MB creatine phosphokinase activity. *Arch. intern. Med.* 136 421 1976
- 8 Smith, A. F. Radford, D. Woeg, C. P. & Oliver M. F.: Creatine kinase MB isoenzyme studies in diagnosis of myocardial infarction. *Brit. Heart J* 38 225 1976.
- 9 Somer H., Dubowitz, V. & Donner M.: Creatine kinase isoenzymes in neuromuscular diseases. *J Neurol. Sci.* 29 129 1976.
- 10 Somer H., Donner M., Murros, J. & Kontinen, A.: A serum isoenzyme study in muscular dystrophy. *Arch. Neurol.* 29 343 1973
- 11 Somer H., Korte, M., Troupp, H. & Kontinen, A.: Brain creatine kinase in blood after acute brain injury. *J Neurol. Neurosurg. Psych.* 38 572, 1975

Bengt W. Johansson: The predictive value is often given to characterize test. But when

doing so, it is important to take into consideration the pertinent patient population

## Are "predictive values" from different patient materials comparable?

S. Hofvendahl, W. Gerhardt, L. Ljungdahl and J. S. Olsen

Dept. of Clinical chemistry and Dept. of Medicine,  
The hospital of Helsingborg, HELSINGBORG, SWEDEN

In recent years, it has become increasingly common to describe the performance of diagnostic test in clinical chemistry in terms of predictive values (1-5). The predictive value of positive test ( $PV_{pos}$ ) in given situation denotes the probability that the patient has the illness in question. Conversely  $PV_{neg}$  expresses the probability that the patient is free from the illness. The use of  $PV$  is of value in different situations, for instance, when evaluating an old test on

new indication or adding a new test to the diagnostic arsenal.

However it is necessary to be aware of some factors that influence the predictive values of diagnostic test in given situation. This article indicates some of these factors against the background of our experiences with new method for the determination of S-CK-B-subunit activity in the diagnosis of acute myocardial infarction (AMI) (2, 3). We first describe model

situation when evaluating a new test in the diagnosis of AMI

The clinician classifies his patients into two groups AMI and non AMI. This classification is based on patient history, clinical symptoms, ECG and routine laboratory data with the exclusion of the new test in question. Fig. 1 is a model of this situation. The clinician looks horizontally from left to right. The AMI-group lies above and the non AMI group below the horizontal line.

The laboratory on the other hand looks at the same diagram in a perpendicular direction from below. The new test can give positive or negative values in relation to a *discriminatory limit* which can be moved (4). The clinician and the chemist meet to decide the value of the new test. The laboratory discovers that even if a positive test result will in most cases, coincide with the clinician's diagnosis of AMI, the analysis occasionally fails. The term *diagnostic sensitivity* describes this situation, the fraction true positive tests of all AMI cases, in the figure expressed as  $P/P$  can vary from 0 to 1. A sensitivity of 0.95 will give a residual fraction  $1 - P$  of 0.05 i.e. 5 per cent false negative tests.

The *diagnostic specificity* of test is expressed as  $Q$  denoting the fraction true negative tests of all non AMI cases. A specificity of 0.95 will thus mean a correct classification of 95 per cent of the non AMI cases. The residual fraction  $1 - Q$  will correspond to 5 per cent false positive tests.

Let us now calculate  $PV_{pos}$  and  $PV_{neg}$ . To do this, we must know the values of

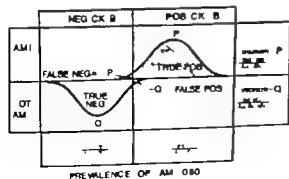


Fig 1

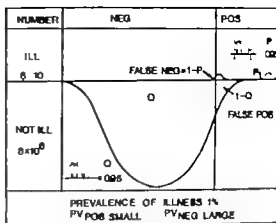


Fig 2

three primary variables, diagnostic sensitivity, diagnostic specificity and the prevalence of disease (AMI) in the actual population. If the AMI and non AMI groups are equal the prevalence of AMI is 0.50.

In a group of 225 patients admitted to the CCU in Helsingborg 106 were subsequently classified as AMI on the basis of traditional diagnostic criteria, corresponding to an AMI prevalence of 0.47. Serial determinations of S-CK B were undertaken in all patients. It was then possible to calculate  $PV_{pos}$  and  $PV_{neg}$  for S-CK B according to the simplified formulas in Fig 1.

We found diagnostic sensitivity to be 0.98 and specificity to be 0.99.  $PV_{pos}$  could be calculated to 0.99 and  $PV_{neg}$  to 0.98. Thus, in our material a positive S-CK B test meant a 99 per cent probability that the patient really had an AMI.

A negative test, on the other hand, meant a 98 per cent probability that the patient was a non AMI.

In a different material of patients with a different prevalence of the disease, the  $PV_{pos}$  and  $PV_{neg}$  will have different values, even if the diagnostic sensitivity and specificity are the same. This might be difficult to understand intuitively. Fig 2 shows an extreme situation. Let us postulate that, in a population of more than 8 million at a given time 80 000 have a certain illness and 8 million have not. This corresponds to a prevalence of the disease of about 1 per cent.

To imagine a diagnostic test in this situation with a sensitivity and specificity of 0.95 would mean 400,000 false positives (5 per cent of 8 million). The true positives, on the other hand, would be 76,000 (95 per cent of 80,000) or less than the false positives.  $PV_{pos}$  falls to only 0.16, despite the test having been performed almost as well as in our series with a  $PV_{pos}$  of 0.99.

The figure also quite clearly illustrates the problems connected to large screening in registries, with traditional tests giving about 5 per cent false positives. Only when "the II" are markedly to the right of the healthy in the diagram can good cost efficiency situation be expected. Fig. 3 is presentation of the numerical values of  $PV_{pos}$  and  $PV_{neg}$  as a function of the prevalence maintaining sensitivity and specificity constant values of 0.95.  $PV_{pos}$  increases with increasing prevalence of AMI. The increase

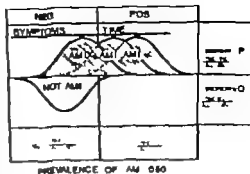


Fig 4

of the test at different time intervals from the onset of infarction. In the diagram, the AMI-prevalence is kept constant at 0.50 and the specificity is 0.95. On admission shortly after onset of symptoms, the proportion of false negative results is relatively high, the sensitivity is low and the specificity is unchanged. Both  $PV_{pos}$  and  $PV_{neg}$  are low.  $PV_{pos}$  increases as a function of time to maximum and then decreases again. This figure thus illustrates the different problems when discussing the value of the tests made either in the admission situation or later when  $PV_{pos}$  is maximum.

To revert to the original situation (Fig. 5) it can finally be mentioned that the values of  $PV_{pos}$  and  $PV_{neg}$  can obviously be manipulated by using different discriminatory limits. If this is moved towards the right, we get higher  $PV_{pos}$  but lower sensitivity and lower  $PV_{neg}$ . If the limit is moved to left,  $PV_{neg}$  increases but  $PV_{pos}$  and specificity fall.

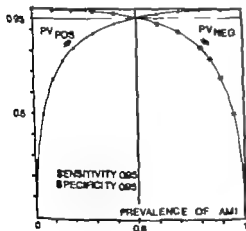


Fig 3

is comparatively large in the prevalence area of 20–30 per cent, for instance, where  $PV_{pos}$  goes from 0.80 to 0.90. When the prevalence varies around 0.5  $PV_{pos}$  and  $PV_{neg}$  change comparatively little.

With given prevalence of AMI and given specificity of the test, change in sensitivity will change  $PV_{pos}$  and  $PV_{neg}$ . Fig. 4 illustrates this by looking at the results

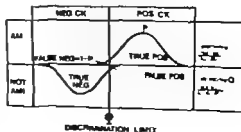


Fig 5

To conclude, we stress the importance of evaluating PV against the patient population in question. PV from populations with different prevalence of disease are obviously not comparable without taking this fact into account. Also different diagnostic situations will influence the PV. The prevalence of AMI in the acute emergency ward will often be lower than that in the CCU. The prevalence of AMI in the CCU again, will depend on the admission policy of the CCU. The prevalence in the CCU will again be different from that of a general medicine ward. The prevalence of a given disease will thus vary with among other factors the different admission policies in different hospitals. It is necessary to take all these factors into account when comparing the PVs calculated in one patient series with those obtained in another.

## Acknowledgement

Grants from the Thorsten and Elsa Segerfalk's Foundation, Helsingborg, Sweden, supported the investigation.

## References

- 1 Bittner J. Die Beurteilung des diagnostischen Wertes klinisch-chemischer Untersuchungen. *J. Clin. Chem. Clin. Biochem.* 15: 1 1977.
- 2 Gerhardt, W., Ljungdahl, L., Hofvendahl, S., Borgesson, J., & Hedenäs, B. Creatine kinase B-subunit activity in human serum I. Development of an immunoinhibition method for routine determination of S-creatine kinase B-subunit activity. *Clin. Chim. Acta* 78: 29 1977.
- 3 Ljungdahl, L., Hofvendahl, S., Gerhardt, W., & Borgesson, J. Creatine kinase B-subunit activity in human serum II. Evaluation of S-CK B-subunit activity in the diagnosis of acute myocardial infarction. *Clin. Chim. Acta* 78: 43 1977.
- 4 Sunderman F. W. Jr. Current concepts of "Normal values", "Reference Values" and "Discrimination Values" in clinical chemistry. *Clin. Chem.* 21: 1873 1975.
- 5 Tarnberg K.-G. Terminologi och diagnostiska test. *Läkartidningen* 73: 1191 1976.
- 6 Wulff H. *Rationel klinik*. Munksgård, Köpenhamn, 1973.

Bengt W. Johansson. New diagnostic aids are of interest and importance as research tools. But are we prepared to include them in routine clinical work? Three questions are of importance in this connection.

1) How reliable are they? Do we have enough experience to use them in routine clinical practice? If so.

2) What information can we get from these new methods that we cannot obtain from those available in routine work today? Are the new methods more reliable? Do we get a diagnostic decision earlier than with today's methods?

3) What are the economical consequences of the introduction of these new methods? What additional equipment and staff will be necessary for the laboratory? These expenses must be weighed against the possible profit in terms of reduced number of beds due to a clear-cut diagnosis earlier than is possible today.

These economical considerations are some of the reasons for a study we have performed in the emergency ward of the Malmö General hospital. Myocardial scintigraphy has been performed in patients suspected of acute myocardial infarction.

# Myocardial scintigraphy in an emergency room

Jan Lessem

Heart section, Dept. of Medicine, General hospital MALMÖ SWEDEN

Myocardial scintigraphy in the emergency room of the department of medicine, Malmö General hospital, was performed in 78 patients suspected of acute myocardial infarction. A mobile gamma camera (General Electric, USA) was used and 10 mCi  $^{99m}\text{Tc}$  pyrophosphate (Diagnostica incorporated, USA) was injected intravenously. All investigations were carried out within ten hours after onset of symptoms. The earliest examinations were made in seven cases 4 hours post-onset of symptoms and in four cases 2 hours post-onset.

All scintigrams were evaluated with regard to presence, localization, and the intensity of an uptake, and were read without knowledge of the clinical diagnosis. Each patient underwent a thorough clinical examination by a physician in charge of the emergency room. ECG and enzymes (S-ALAT and S-ASAT) were sampled twice with an interval of 6 hours. A pure clinical decision was then taken about the cause of the discomfort. When making his decision, the physician had no knowledge of the outcome of the scintigraphy.

- Three groups emerged
1. Those believed clinically to have an acute myocardial infarction and therefore referred to the coronary care unit: 28 patients.
  2. Those believed to have causes other than coronary disease for the chest pain and admitted to other wards in the department of medicine: 10 patients.
  3. Those believed to have any underlying cardiac disorder causing their chest pain and thus were sent home: 40 patients.
- Those admitted to the coronary care unit or sent home were later re-examined scintigraphically with 1.5 mCi  $^{99m}\text{Tl}$  (Philips Daphar the Netherlands) to detect any perfusion defects.

Of the 28 patients admitted to the coro-

nary care unit, 23 had shown pyrophosphate uptake in the emergency room. Of these, 15 were well localized and showed an intensity exceeding 11% of the 23 also exhibited perfusion defects when re-examined and 17 of them were later discharged with a diagnosis of acute transmural myocardial infarction. 3 were discharged with the diagnosis unstable angina pectoris the other 3 were discharged with the diagnosis other than cardiac. 5 patients, admitted to the coronary care unit, had exhibited negative pyrophosphate scintigrams in the emergency room. None of these 5 later showed any perfusion defect. All were discharged with the diagnosis non-cardiac disorders.

Of the 40 patients sent home, 26 had negative pyrophosphate examinations. 23 of these showed negative Tl when re-examined. The one patient with a Tl perfusion defect had suffered a previous apical infarct. However 14 patients with positive pyrophosphate scintigrams were sent home. Intensity of the uptake in only one of the 14 exceeded one. This patient later developed an acute myocardial infarction. When the 14 patients were re-examined with  $^{99m}\text{Tl}$ , it was found that 10 showed perfusion defects the other 4 had no perfusion defects (Table I).

From this study it can be concluded that myocardial scintigraphy with  $^{99m}\text{Tc}$  pyrophosphate yields positive results, before conventional laboratory methods, which in turn might lead to other therapy being started earlier. It is then possible that more myocardium can be saved from final necrosis.

Furthermore, negative pyrophosphate scan in the emergency room would add to the clinical confidence in sending the patients home. However a positive scintigram with an intensity above the lowest should be warning and lead to admission to a coronary care unit.

To conclude we stress the importance of evaluating PV against the patient population in question. PV from populations with different prevalence of disease are obviously not comparable without taking this fact into account. Also different diagnostic situations will influence the PV. The prevalence of AMI in the acute emergency ward will often be lower than that in the CCU. The prevalence of AMI in the CCU again will depend on the admission policy of the CCU. The prevalence in the CCU will again be different from that of a general medicine ward. The prevalence of a given disease will thus vary with, among other factors, the different admission policies in different hospitals. It is necessary to take all these factors into account when comparing the PVs calculated in one patient series with those obtained in another.

### Acknowledgement

Grants from the Thorsten and Elsa Segerfalks Foundation, Helsingborg, Sweden, supported the investigation.

Bengt W. Johansson: New diagnostic aids are of interest and importance as research tools. But are we prepared to include them in routine clinical work? Three questions are of importance in this connection.

1) How reliable are they? Do we have enough experience to use them in routine clinical practice? If so

2) What information can we get from these new methods that we cannot obtain from those available in routine work today? Are the new methods more reliable? Do we get a diagnostic decision earlier than with today's methods?

### References

- 1 Blättner J. Die Beurteilung des diagnostischen Wertes klinisch-chemischer Untersuchungen. *J Clin Chem. Clin Biochem* 15: 1 1977
- 2 Gerhardt, W., Ljungdahl L., Hofvendahl, S., Börjesson J. & Hedenäs, B. Creatine kinase B-subunit activity in human serum I. Development of an immunoinhibition method for routine determination of S-creatine kinase B-subunit activity. *Clin. Chim. Acta* 78: 29 1977
- 3 Ljungdahl L., Hofvendahl S., Gerhardt, W., & Börjesson, J. Creatine kinase B-subunit activity in human serum II. Evaluation of S-CK B-subunit activity in the diagnosis of acute myocardial infarction. *Clin. Chim. Acta* 78: 43 1977
- 4 Sunderman, F. W. Jr. Current concepts of "Normal values" "Reference Values and Discrimination Values" in clinical chemistry. *Clin. Chem* 21: 1873 1975
- 5 Tarnberg, K.-G. Terminologi och diagnostiska test. *Läkartidningen* 73: 1191 1976
- 6 Wulff H. *Rationel klinik*. Munksgaard, Copenhagen, 1973

3) What are the economical consequences of the introduction of these new methods? What additional equipment and staff will be necessary for the laboratory? These expenses must be weighed against the possible profit in terms of reduced number of beds due to a clear-cut diagnosis earlier than is possible today.

These economical considerations are some of the reasons for a study we have performed in the emergency ward of the Malmö General hospital. Myocardial scintigraphy has been performed in patients suspected of acute myocardial infarction.

# Myocardial scintigraphy in an emergency room

Jan Lessem

Heart section, Dept. of Medicine, General hospital, MALMÖ SWEDEN

Myocardial scintigraphy in the emergency room of the department of medicine, Malmö General hospital, was performed in 78 patients suspected of acute myocardial infarction. A mobile gamma camera (General Electric, USA) was used and 10 mCi  $^{99m}\text{Tc}$  pyrophosphate (Diagnosics incorporated, USA) was injected intravenously. All investigations were carried out within ten hours after onset of symptoms. The earliest examinations were made in seven cases 4 hours post-onset of symptoms and in four cases 2 hours post-onset.

All scintigrams were evaluated with regard to presence, localization, and the intensity of a uptake, and were read without knowledge of the clinical diagnosis. Each patient underwent a thorough clinical examination by a physician in charge of the emergency room. ECG and enzymes (S-ALAT and S-ASAT) were sampled twice with an interval of 6 hours. A final clinical decision was then taken about the cause of the discomfort. When making his decision, the physician had no knowledge of the outcome of the scintigraphy.

Three groups emerged

1. Those believed clinically to have an acute myocardial infarction and therefore referred to the coronary care unit: 28 patients.
2. Those believed to have causes other than coronary disease for the chest pain and admitted to other wards in the department of medicine: 10 patients.
3. Those believed to have any underlying cardiac disorder causing their chest pain and thus were sent home: 40 patients.

Those admitted to the coronary care unit or sent home were later re-examined scintigraphically with 1.5 mCi  $^{201}\text{Tl}$  (Philips Duphar, the Netherlands) to detect any perfusion defects.

Of the 28 patients admitted to the coronary

care unit, 23 had shown pyrophosphate uptake in the emergency room. Of these, 15 were well localized and showed an intensity exceeding 118 of the III also exhibited perfusion defects when re-examined and 17 of them were later discharged with a diagnosis of acute transmural myocardial infarction. 3 were discharged with the diagnosis unstable angina pectoris the other 3 were discharged with the diagnosis other than cardiac. 5 patients, admitted to the coronary care unit, had exhibited negative pyrophosphate scintigrams in the emergency room. None of these 5 later showed any perfusion defect. All were discharged with the diagnosis non-cardiac disorders.

Of the 40 patients sent home, 26 had negative pyrophosphate examinations; 25 of them showed negative Tl when re-examined. The one patient with Tl perfusion defect had suffered a previous apical infarct. However 14 patients with positive pyrophosphate scintigrams were sent home. Intensity of the uptake in only one of the 14 exceeded one. This patient later developed an acute myocardial infarction. When the 14 patients were re-examined with  $^{201}\text{Tl}$ , it was found that 10 showed perfusion defects the other 4 had no perfusion defects (Table I).

From this study it can be concluded that myocardial scintigraphy with  $^{99m}\text{Tc}$  pyrophosphate yields positive results, before conventional laboratory methods, which in turn might lead to other therapy being started earlier. It is then possible that more myocardium can be saved from final necrosis.

Furthermore, negative pyrophosphate scan in the emergency room would add to the clinical confidence in sending the patients home. However positive scintigrams with an intensity above the lowest should be warning and lead to admission to a coronary care unit.



To conclude, we stress the importance of evaluating PV against the patient population in question. PV from populations with different prevalence of disease are obviously not comparable without taking this fact into account. Also different diagnostic situations will influence the PV. The prevalence of AMI in the acute emergency ward will often be lower than that in the CCU. The prevalence of AMI in the CCU again, will depend on the admission policy of the CCU. The prevalence in the CCU will again be different from that of a general medicine ward. The prevalence of a given disease will thus vary with, among other factors, the different admission policies in different hospitals. It is necessary to take all these factors into account when comparing the PVs calculated in one patient series with those obtained in another.

### Acknowledgement

Grants from Thorsten and Elsa Segerfalk's Foundation, Helsingborg, Sweden, supported the investigation.

### References

1. Büttner J. Die Beurteilung des diagnostischen Wertes klinisch-chemischer Untersuchungen. *J. Clin. Chem. Clin. Biochem.* 15: 1 1977.
2. Gerhardt, W., Ljungdahl, L., Hofvendahl, S., Börjesson, J. & Hedenäs, B. Creatine kinase B-subunit activity in human serum I. Development of an immunoinhibition method for routine determination of S-creatine kinase B-subunit activity. *Clin. Chim. Acta* 78: 29 1977.
3. Ljungdahl, L., Hofvendahl, S., Gerhardt, W., & Börjesson, J. Creatine kinase B-subunit activity in human serum II. Evaluation of S-CK B-subunit activity in the diagnosis of acute myocardial infarction. *Clin. Chim. Acta* 78: 43 1977.
4. Sunderman F. W. Jr. Current concepts of "Normal values", "Reference Values" and "Discrimination Values" in clinical chemistry. *Clin. Chem.* 21: 1873 1975.
5. Tarnberg K. G. Terminologi och diagnostiska test. *Läkarskningen* 73: 1191 1976.
6. Wulff H. *Rationel klinik*. Munksgaard, København, 1973.

*Bengt W. Johansson*. New diagnostic aids are of interest and importance as research tools. But are we prepared to include them in routine clinical work? Three questions are of importance in this connection.

1) How reliable are they? Do we have enough experience to use them in routine clinical practice? If so

2) What information can we get from these new methods that we cannot obtain from those available in routine work today? Are the new methods more reliable? Do we get a diagnostic decision earlier than with today's methods?

3) What are the economical consequences of the introduction of these new methods? What additional equipment and staff will be necessary for the laboratory? These expenses must be weighed against the possible profit in terms of reduced number of beds due to a clear-cut diagnosis earlier than is possible today.

These economical considerations are some of the reasons for a study we have performed in the emergency ward of the Malmö General hospital. Myocardial scintigraphy has been performed in patients suspected of acute myocardial infarction.

# Mycardial scintigraphy in an emergency room

Jan Lessem

Heart section, Dept. of Medicine, General hospital MALMÖ SWEDEN

Mycardial scintigraphy in the emergency room of the department of medicine, Malmö General hospital, was performed in 78 patients suspected of acute myocardial infarction. A mobile gamma camera (General Electric, USA) was used and 10 mCi  $^{99m}\text{Tc}$  pyrophosphate (Diagnostica Incorporated, USA) was injected intravenously. All investigations were carried out within ten hours after onset of symptoms. The earliest examinations were made in seven cases 4 hours post-onset of symptoms and in four cases 2 hours post-onset.

All scintigrams were evaluated with regard to presence, localization, and the intensity of an uptake, and were read without knowledge of the clinical diagnosis. Each patient underwent a thorough clinical examination by physician in charge of the emergency room. ECG and enzymes (S-ALAT and S-ASAT) were sampled twice with an interval of 6 hours. A pure clinical decision was then taken about the cause of the discomfort. When making his decision, the physician had no knowledge of the outcome of the scintigraphy.

Three groups emerged

1. Those believed clinically to have an acute myocardial infarction and therefore referred to the coronary care unit: 28 patients.
2. Those believed to have causes other than coronary disease for the chest pain and admitted to other wards in the department of medicine: 10 patients.
3. Those believed to have any underlying cardiac disorder causing their chest pain and thus were sent home: 40 patients.

Those admitted to the coronary care unit or sent home were later re-examined scintigraphically with 1.5 mCi  $^{201}\text{Tl}$  (Philips Duphar, the Netherlands) to detect any perfusion defects.

Of the 28 patients admitted to the coronary

care unit, 23 had shown pyrophosphate uptake in the emergency room. Of these, 15 were well localized and showed an intensity exceeding 118 of the 23 also exhibited perfusion defects when re-examined and 17 of them were later discharged with a diagnosis of acute transmural myocardial infarction. 3 were discharged with the diagnosis unstable angina pectoris, the other 3 were discharged with the diagnosis other than cardiac. 5 patients, admitted to the coronary care unit, had exhibited negative pyrophosphate scintigrams in the emergency room. None of these 5 later showed any perfusion defect. All were discharged with the diagnosis non-cardiac disorders.

Of the 40 patients sent home, 26 had negative pyrophosphate examinations. 25 of them showed negative Tl when re-examined. The one patient with Tl perfusion defect had suffered a previous apical infarct. However 14 patients with positive pyrophosphate scintigrams were sent home. Intensity of the uptake in only one of the 14 exceeded one. This patient later developed an acute myocardial infarction. When the 14 patients were re-examined with  $^{201}\text{Tl}$ , it was found that 10 showed perfusion defects, the other 4 had no perfusion defects (Table I).

From this study it can be concluded that myocardial scintigraphy with  $^{99m}\text{Tc}$  pyrophosphate yields positive results, before conventional laboratory methods, which in turn might lead to other therapy being started earlier. It is then possible that more myocardium can be saved from final necrosis.

Furthermore, negative pyrophosphate scan in the emergency room would add to the clinical confidence in sending the patients home. However, positive scintigram with an intensity above the lowest should be a warning and lead to admission to a coronary care unit.

**Table 1**

*This table shows the difference between scintigraphical results with both pyrophosphate and Thallium and discharged diagnosis*

<i>Outcome of scintigraphy</i>		<i>Diagnoses when discharged</i>	
Positive pyrophosphate	}	1	AMI between examinations
positive Tl		2	old AMI and aneurysm
		4	unstable angina pectoris
		3	chest pain of unknown origin
Positive pyrophosphate	}	3	unstable angina
negative Tl		1	chest pain of unknown origin

*J Fucher Hansen* What was the outcome of those patients who were sent home, but had a positive scintigraphy? Did they have an acute myocardial infarction?

*J Lessem* Of those sent home with a positive  $^{99m}\text{Tc}$  pyrophosphate scintigram, two later returned with verified acute myocardial infarcts. In six patients, we also found perfusion defects when re-examined with  $^{201}\text{Tl}$ . The significance of this finding is not clear. It indicates that a perfusion defect is present, but its age cannot be stated. Therefore we are still uncertain whether these patients had an infarct when they came to the emergency room, but there is at least the suggestion that they might have had. The prognosis in this group of patients was unchanged.

*B Scherstén* What was the clinical advantage of the scintigrams? Could they be used as a prognostic tool?

*J Lessem* To answer the first question: In our emergency ward study a negative scintigram never gave a false result. Myocardial scintigraphy could possibly result in a more rational use of CCU beds.

To answer the second question: Yes, to a certain extent, but our study was not planned as a true prognostic study.

*P F Høiland-Carlson* What is the latest time after an infarction when the Tc pyrophosphate scintigram can be expected still to be positive?

*J Lessem* Usually 10–14 days after onset of symptoms. But at that late date, the intensity of the uptake is less than during the acute phase. If an aneurysm develops, a positive uptake might remain a long time after onset of symptoms.

*S Persson* Would you wait 10 hours after the onset of symptoms to do a Tc pyrophosphate scintigram?

*J Lessem* No. In principle, patients with a negative scintigram can be sent home.

*E Sandoe* Is it possible from Tc pyrophosphate scintigraphy to decide whether a thoracic pain is a sign of impending myocardial infarction?

*J Lessem* It is not possible to diagnose with either scintigraphy or any other method whether a true myocardial infarction will develop in these patients.

*B W Johansson* What are the indications for myocardial scintigraphy in the emergency ward? Is negative scintigraphy with  $^{201}\text{Tl}$  or positive imaging with  $^{99m}\text{Tc}$  pyrophosphate preferable?

*J Lessem* One indication could be to select more suitable patients for the coronary care units than has previously been done. However myocardial scintigraphy should not be used alone in deciding the future of the patients, but should only be regarded as a compliment to other investigatory methods. It is still uncertain whether ischaemic

mic patients can be diagnosed with either Thallium or pyrophosphate in the emergency room, but if this is so, a more aggressive therapy might be instituted earlier. In the emergency room, it seems as though pyrophosphate is superior to Thallium; it cannot separate an old infarct from a new event. Re-infarcts can, for example, be very difficult to diagnose with Thallium.

**Bengt W. Johansson** The ECG is often of minor help for the diagnosis of acute myocardial infarction in patients with an artificial pacemaker. Myocardial scintigraphy should be of assistance in these patients, provided the tissue reaction to the electrode does not induce false positive findings. Experiences from 10 pacemaker patients without any clinical or laboratory signs of acute infarction show no positron uptake with  $^{201}\text{Tl}$  pyrophosphate, indicating that myocardial imaging is of diagnostic value in these patients.

Is determination of myoglobin in the urine or serum of diagnostic value in patients in the emergency ward or in patients seen by the doctor outside the hospital?

**Bengt Schersten** The methods available today have not been sufficiently documented to defend their introduction in routine clinical work.

**Jean Laine** A teststrip with reaction based on the ability of myoglobin, excreted in urine, to act as peroxidase has been tested in 62 patients with suspected acute myocardial infarction. Thirtyfive developed an infarct and the strip turned positive in only 18, of whom three were positive before ECG and enzyme rise. In 27 patients with no myocardial infarction only two positive teststrips were found. The sensitivity of the strip was thus calculated to be 52 %, whereas specificity was found to be 93 %.

**V. Haursten** Most of the discussion has concerned scintigraphy and improved enzymatic diagnosis of acute infarction. Would it not be possible to get more information from the ECG? The ECG is highly

specific; it also provides a large amount of false negative findings. Is it possible to improve the diagnostic ECG sensitivity by using other leads, such as orthogonal Frank leads or vectorcardiography?

**J. Kyte** ECG is an empirical method, and we compare the ECG of a patient with ECG criteria considered to be normal. We will, of course, observe many false negative ECG. As yet, we still know too little about the forward problem relating intracardiac events to the shape of the ECG to use it as a quantitative predictor. Because individual differences in the electrode distance and orientation to the infarct, differences in the geometry and conductivity of the chest, and variations in skin resistance, quantitative comparisons among patients are invalidated. The orthogonal leads compensate for some of these problems; this offers more sensitivity in the diagnosis. Vector loop analysis takes into consideration the spatial distribution of the electrocardiographic events and not only changes in peak amplitude of QRS waves.

Especially by recording the vectorcardiograms sequentially during the evolution of an infarct, small changes are readily obtained. Furthermore, multiple recordings of the vectorcardiogram can be used to construct a curve that reflects the immediate development of the infarct. This could be of potential value in the future.

**Bengt W. Johansson** What diagnostic criteria should we use in the diagnosis of acute myocardial infarction? Although differences exist between hospitals, I think many keep more or less strictly to the following criteria:

- 1 Central chest pain, pulmonary edema, syncope or shock.
- 2 Appearance of a pathological Q wave and/or appearance or disappearance of localized ST elevation followed by T wave inversion in two or more leads of 12 lead ECG.
- 3 Two elevated ASAT values with a peak about 24 hours after onset of symptoms

**Table 1**

*This table shows the difference between scintigraphical results with both pyrophosphate and Thallium and discharged diagnosis*

Outcome of scintigraphy		Diagnoses when discharged	
Positive pyrophosphate	}	1 AMI between examinations	10
positive Tl		2 old AMI and aneurysm	
		4 unstable angina pectoris	
		3 chest pain of unknown origin	
Positive pyrophosphate	}	3 unstable angina	4
negative Tl		1 chest pain of unknown origin	

*J Fischer Hansen* What was the outcome of those patients who were sent home, but had a positive scintigraphy? Did they have an acute myocardial infarction?

*J Lessem* Of those sent home with a positive  $^{99m}\text{Tc}$ -pyrophosphate scintigram, two later returned with verified acute myocardial infarcts. In six patients, we also found perfusion defects when re-examined with  $^{201}\text{Tl}$ . The significance of this finding is not clear. It indicates that a perfusion defect is present, but its age cannot be stated. Therefore we are still uncertain whether these patients had an infarct when they came to the emergency room, but there is at least the suggestion that they might have had. The prognosis in this group of patients was unchanged.

*B Scherstén* What was the clinical advantage of the scintigrams? Could they be used as a prognostic tool?

*J Lessem* To answer the first question. In our emergency ward study a negative scintigram never gave a false result. Myocardial scintigraphy could possibly result in a more rational use of CCU beds.

To answer the second question. Yes, to a certain extent, but our study was not planned as a true prognostic study.

*P F Houland-Carlson* What is the latest time after an infarction when the Tc pyrophosphate scintigram can be expected still to be positive?

*J Lessem* Usually 10–14 days after onset of symptoms. But at that late date, the intensity of the uptake is less than during the acute phase. If an aneurysm develops, a positive uptake might remain a long time after onset of symptoms.

*S Persson* Would you wait 10 hours after the onset of symptoms to do a Tc pyrophosphate scintigram?

*J Lessem* No. In principle, patients with a negative scintigram can be sent home.

*E Sandoe* Is it possible from Tc pyrophosphate scintigraphy to decide whether a thoracic pain is a sign of impending myocardial infarction?

*J Lessem* It is not possible to diagnose with either scintigraphy or any other method whether a true myocardial infarction will develop in these patients.

*B W Johansson* What are the indications for myocardial scintigraphy in the emergency ward? Is negative scintigraphy with  $^{201}\text{Tl}$  or positive imaging with  $^{99m}\text{Tc}$  pyrophosphate preferable?

*J Lessem* One indication could be to select more suitable patients for the coronary care units than has previously been done. However myocardial scintigraphy should not be used alone in deciding the future of the patients, but should only be regarded as a complement to other investigatory methods. It is still uncertain whether ischaemic

**K. E. Green** Does S-CK and/or myoglobin increase in connection with a virus myositis and/or myocarditis?

**L. Malmberg** Enzymes were not checked routinely during the acute phase in our patients with viral myocarditis, but it is conceivable that myocardial necrosis produced by a myocarditis would cause a rise in S-CK-MB.

**B. Scherström** As far as I know the literature contains no reports that give an unambiguous answer to this question.

**M. Herlitz** From a laboratory point of view it would be advantageous if the clinicians used more strict criteria for the diagnosis of acute myocardial infarction as far as the enzymes CK, ASAT, ALAT and LD are concerned, including standardized sampling times in relation to onset of symptoms. Ninety per cent of the Nordic laboratories use the standardized Nordic enzyme methods for analysis of these enzymes.

**B. Brörck** I have listened with interest to the questions and, as often happens, they have provoked some heretical thoughts in my mind. Is this refined diagnosis mainly *art pour art* or does it really mean something to our decision making for the patient? Our Chairman and Doctor Scherström have both touched upon this matter but being somewhat older I may also have the privilege of being slightly more radical.

What does it mean in practical terms to make diagnosis of acute myocardial infarction in a patient? Any diagnosis carries with it prognosis (or even two) one immediate which may require instantaneous decisions and one long-term (if the patient survives), implying advice with regard to mode of life, employment, life insurance etc. — that is to say psychological loads.

Therapy depends on prognosis in self-limiting diseases with favourable prognosis therapy is often neither needed nor available, as in some dermatological diseases.

Now what is the difference between therapy on the basis of symptomatology alone, or on the basis of diagnosis? The function of a diagnosis is to indicate subpopulation among all who appear to have a relevant symptomatology — namely those who fit a set of more or less rigid criteria. I would estimate that the refined diagnoses presented here might increase the size of the subpopulation by a few per cent, perhaps from 95 to 99 per cent.

But it is *per se* possible that the prognosis for the diagnostically selected subpopulation is comparable to the prognosis also for one or more other subpopulations who, for one or other reason, do not completely fit the criteria and thus fall outside the borders of the criteria.

Now it is conceivable that the assessment of the clinical symptomatology — for the experienced physician — might be as good a prognostic indication as that based on refined laboratory diagnostics. Could it therefore be of interest to organize further studies of the value of refined diagnostic procedures in a way that might permit a comparison with the early clinical judgement, from the prognostic point of view? I would suggest that this possibility be given consideration in the lay-out of further studies. One reason why I urge you to consider this possibility is my feeling that while diagnosis and therapy have made great progress in recent decades, prognosis has advanced very little — as applied to the individual case. We have massive series of epidemiological and other statistical data, but we are still very much at loss when judging the specific individual patient. In our department, we have for some time engaged in a project of early clinical prognostication in acute myocardial infarction by physicians and nurses in the CCU and we hope that the experience derived from a comparison of our "best" with the later verification by the patient's fate might help to improve our ability to make proper prognostic judgements.

in combination with a peak ALAT value about 36 hours after onset of symptoms and lower than the ASAT peak. Alternatively one elevated ASAT value in combination with one elevated LD value with a peak about three days after onset of symptoms.

- 4 Myocardial necrosis at autopsy of an age co responding to the onset of symptoms.

Criterion 4 or a combination of two of criteria 1 2 and 3 are necessary for the diagnosis of acute myocardial infarction.

Are we prepared today to revise or change these diagnostic criteria?

*S Hofvendahl* We use the following routine. S-CK and S-CK MB three times a day S-ASAT and S-ALAT once a day and S-LD once a day until maximal value has been passed. S-CK MB and S-LD isoenzymes provide a cardiospecific enzyme combination that covers a maximum time interval. In addition, S-ASAT and S-ALAT have a place in the diagnostic arsenal they are well documented and not costly. They provide a simple estimate of the degree of possible liver involvement, which is of clinical value. Furthermore, it is possible that microinfarctions are more readily diagnosed with the sensitive S-ASAT than with other methods.

*A Pedersen* Based on the enzyme findings in 1300 patients out of whom 900 had an acute myocardial infarction, our routine in Glostrup has included only S-CK MB, unless there is reason to suspect that the infarction occurred more than 36 hours before the blood sample is taken. If so we determine in addition S-ASAT S-ALAT and S-LD and in selected cases an LD electrophoresis is done.

S-CK MB is analysed electrophoretically. The MB fraction can be completely isolated, and the specificity is close to 100 %.

This routine requires certain laboratory efforts, but the laboratory is also relieved of the other enzyme analyses, and the necessary costs are certainly lower than for myocardial scintigraphy.

*E Lorentzen* As the S-CK peak is of shorter duration than that of S-ASAT is it not reasonable to prefer S-ASAT? We still have little experience of the new methods. New sources of error still appear. This is true, for example, in the serial determination of S-CK for evaluation of infarct size (Editorial Circulation 52 1 1975). I will therefore make a plea to wait to include these new methods in the routine diagnosis of acute infarction until we have gained more experiences and well founded results showing that they actually represent true progress.

*C Müller* Is there any place for S-CK MB in the diagnosis of acute myocardial infarction during or after cardiac surgery? Previous methods including enzymes are often unreliable. Is there a difference in the S-CK MB response after an uncomplicated cardiectomy and an aorto-coronary by-pass? Can an increase of S-CK MB postoperatively be regarded as an expression of an acute myocardial infarction?

*S Ström* Frequent CK MB determinations in 25 consecutive cases of coronary by-pass operations with mammary artery or saphenous vein show that CK MB in serum is found in all patients postoperatively with a wide range of maximum values. Myocardial infarction could not be diagnosed in any of these patients with conventional methods and the CK MB curve postoperatively differs from that seen after an infarction with a maximum in direct connection to the operation. Drainage of the right atrium, which is routinely done during these operations, produces myocardial damage, but it is small and should be of the same magnitude in all patients. There is a correlation between CK MB level and the duration of extracorporeal circulation and aortic clamping, that is to say between enzyme release and the amount of ischaemia.

*J Lessem* Tc pyrophosphate scintigraphy is of great value in the diagnosis of pre and postoperative myocardial infarction.

K. E. Grotte. Does S-CK and/or myoglobin increase in connection with a virus myositis and/or myocarditis?

L. Malmberg. Enzymes were not checked routinely during the acute phase in our patients with viral myocarditis, but it is conceivable that myocardial necrosis produced by a myocarditis would cause a rise in S-CK MB.

B. Scherstin. As far as I know the literature contains no reports that give an unambiguous answer to this question.

M. Herder. From laboratory point of view it would be advantageous if the clinicians used more strict criteria for the diagnosis of acute myocardial infarction as far as the enzymes CK, ASAT, ALAT and LD are concerned, including standardized sampling times in relation to onset of symptoms. Ninety per cent of the Nordic laboratories use the standardized Nordic enzyme methods for analysis of these enzymes.

G. Björck. I have listened with interest to the questions and, as often happens, they have provoked some heretical thoughts in my mind. This refined diagnostics mainly *l'art pour l'art* or does it really mean something to our decision making for the patient? Our Chairman and Doctor Scherstin have both touched upon this matter but being somewhat older I may also have the privilege of being slightly more radical.

What does it mean in practical terms to make diagnosis of acute myocardial infarction in a patient? Any diagnosis carries with it prognosis (or even two) one immediate which may require instantaneous decisions and one long-term (if the patient survives), implying advice with regard to mode of life, employment, life insurance etc. — that is to say psychological loads.

Therapy depends on prognosis in self-limiting diseases with favourable prognosis therapy is often neither needed nor available as in some dermatological diseases.

Now what is the difference between therapy on the basis of symptomatology alone, or on the basis of diagnostics? The function of a diagnosis is to indicate a subpopulation among all who appear to have a relevant symptomatology — namely those who fit a set of more or less rigid criteria. I would estimate that the refined diagnostics presented here might increase the size of the subpopulation by a few per cent, perhaps from 95 to 99 per cent.

But it is *per se* possible that the prognosis for the diagnostically selected subpopulation is comparable to the prognosis also for one or more other subpopulations who, for one or other reason, do not completely fit the criteria and thus fall outside the borders of the criteria.

Now it is conceivable that the assessment of the clinical symptomatology — for the experienced physician — might be as good a prognostic indication as that based on refined laboratory diagnostics. Could it therefore be of interest to organize further studies of the value of refined diagnostic procedures in a way that might permit comparison with the early clinical judgement, from the prognostic point of view? I would suggest that this possibility be given consideration in the lay-out of further studies. One reason why I urge you to consider this possibility is my feeling that while diagnosis and therapy have made great progress in recent decades, prognosis has advanced very little — as applied to the individual case. We have massive series of epidemiological and other statistical data, but we are still very much at loss when judging the specific individual patient. In our department, we have for some time engaged in a project of early clinical prognostication in acute myocardial infarction by physicians and nurses in the CCU and we hope that the experience derived from comparison of our "beta" with the later verification by the patient's fate might help to improve our ability to make proper prognostic judgements.



*Bengt W Johansson* It is often difficult to get a definite diagnosis in patients who die soon after the onset of symptoms. An autopsy might reveal a pulmonary embolus or a cerebral haemorrhage. An acute myocardial infarction takes several hours to produce clear-cut gross or microscopical changes. Half of the patients leaving hospital after treatment of an acute infarction die suddenly. This can be due to a ventricular fibrillation without an infarction; it can also be due to an acute infarction, and the

time might have been too short for a coronary thrombus to develop. The coronary circulation during ventricular fibrillation will drop to almost zero with subsequent myocardial changes. It takes some time for the infarct to become manifest, although a decrease in potassium and an increase in sodium and calcium concentrations have been reported to occur a few minutes after the coronary circulation has stopped. These problems are especially relevant in forensic medicine.

## The diagnostic of fresh ischaemic lesions in forensic pathology

Gerhard E Voigt

Dept. of Forensic Medicine, University of Lund, LUND SWEDEN

Sudden and unexpected death dominates the autopsy material of Departments of Forensic Medicine. Heart disease is the most common cause. By gross examination, it is difficult to differentiate such cases from intoxications with medicaments such as sleeping pills, tranquilizers, or analgetics, often in combination with alcohol. These intoxications do not cause specific morphological changes and can easily be overlooked, as can an early myocardial infarction. To select the cases demanding toxicologic chemical analysis, it is most important to have methods to verify the early stages of myocardial ischaemia, indicating that the cause of death was cardiovascular.

In our experience the heart dissection technique during autopsy is important for visualizing early stages of infarction. Thus the left ventricle is opened by a cut at the left margin of the heart running through the mitral valve. From this cut, another is made with scissors to the aorta, leaving a small part of the wall of the left ventricle between the two cuts. The wall of the left ventricle is then stretched open and its thickness is halved, beginning at the apex of the heart and continuing to the level of

the coronary sulcus. It is important not to wash the heart before investigating the cut surface. A fresh infarction has a prominent cut surface, but there is often no difference in the colour between the ischaemic and non-affected parts of the muscle. It is almost impossible to see fresh infarctions on small cut surfaces. Concerning further investigations to verify fresh myocardial infarction Knight has recently surveyed reliable methods. He recommends for the most part histochemical enzyme methods (malate dehydrogenase) and describes SDH and LDH as useful tests. For two reasons, we cannot use such methods as routine tests:

- 1) Many of our cases have a variable degree of autolysis making it impossible to obtain reliable results,
- 2) For a department with a large autopsy load (2200/year) and a small medical and technical staff the histochemical methods are too time-consuming. Thus, we need simple methods that provide reliable results also on decomposed material.

At our department, the Mallory PTAH stain has been chosen to visualize ischaemic myocardial lesions that can be overlooked

in haematoxylin and eosin stained slices. We have used this method for about 12 years in several thousand cases. To achieve satisfactory staining results, the following is necessary:

1. The tissue pieces preserved at autopsy for fixation in a 6—10 per cent formalin physiological saline solution must not be much larger than the later paraffin embedded material. The volume of the fixative must be more than 20 times that of the tissue. In microscopic sections from material fixed in a crushed piece and in too little formalin, the PTAH-method, excepting marginal areas, stains the muscle fibres red dish instead of intensive blue-violet.

2. 2 per cent potassium permanganate and 1 per cent oxalic acid solution must be freshly prepared before use.

With this method, the first sign of an ischaemic lesion is a patchy change in the width of the normal striation. In later stages, there appear broad bands and granules with deep blue-violet colour which contrast well with the reddish-stained cytoplasmic background. Later these bands and granules disappear and the injured muscle fibres stain only red. In this stage, inflammatory cell infiltration is often visible.

This method allows no more to be seen than in haematoxylin and eosin stained sections, but the PTAH method makes it easier to detect ischaemic lesions and affords considerable security in the microscopical analysis. I material decomposed by autolysis, the PTAH-method, in our experience, is the stain of choice, especially when haematoxylin and eosin staining does not give reliable results.

A secular dependent hypoxaemia or ischaemia does not, in general, result in immediate morphological changes. I fresh infarctions, there are nearly always various stages of change in groups of myocardial fibres. Thus if in case of sudden unexpected death, some groups of changed muscle fibres are found in the sections, this strongly indicates that death was due to cardiac causes. This finding must, of course, be interpreted in relation to the other autopsy

findings. A very important finding is haemorrhage in an arteriosclerotic plaque. Thrombosis in cases of fresh ischaemic lesions occurs only exceptionally.

Another method of visualizing fresh ischaemic myocardial lesions, discussed several times in the literature is the HBFP (haematoxylin basic fuchsin-picric acid)-stain according to Lie *et al.* The method seems to be technically easy to perform. In improving upon this method, the following observations have been made:

If a series of sections of the same material are stained on one slide, and the slide in the different baths remains upright, difference in the staining result occurs between the sections on the top and those on bottom of the slide. This indicates that the method does not quite give reproducible results.

In the method according to Lie, the sections are transferred after staining in an aqueous basic fuchsin solution to water to acetone, and to a bath consisting of picric acid and acetone, where the red colour (basic fuchsin) runs off the sections. It is desired that only the muscle striations within ischaemic lesions remain stained.

According to this method, the sections are not dehydrated before treating with acetone-picric acid. It can be supposed that water-free picric acid extracts the dye-containing water from the sections. If the sections, after staining with basic fuchsin, are dehydrated by drying with filter paper and immersion in baths of methyl benzoate (which extracts only water and leaves the dye in the section) followed by treatment in xylol acetone and afterwards immersed in solution of water-free picric acid acetone, the decoloration of the section takes some time. But this process can be quickly expedited if the sections are removed from the bath, hydrated with breath moisture, and quickly returned to the solution. Thus it would appear that the water content of the sections is the most important factor in achieving the desired results. Ischaemic muscle fibres probably have a greater density than uninjured muscle fibres. The affi-

nity of the ischaemic structures to water containing fuchsin is thereby somewhat greater than the affinity of uninjured structures. But the difference between the affinities is so small that it seems impossible to carry out the method in such a way that only ischaemic lesions can be visualized. This method is therefore of no value in the routine work.

To summarise The PTAH method, if handled technically correctly is in our experience the method of choice with which easily to visualize fresh ischaemic lesions in the myocardium.

## References

- Knight, H. Investigation of sudden deaths from myocardial ischaemia. *Forensic Science* 8 33 1976
- Lie, J. T., K. E. Holley W. R. Kampa and J. L. Titus. New histochemical method for morphological diagnosis of early stages of myocardial ischaemia. *Mayo Clin. Proc.* 46 319 1971
- Voigt, G. E. Zur Diagnostik frischer Myocardinfarctionen. *Dtsch. Z. ges. gerichtl. Med.* 59 113 1967





# Acta Medica Scandinavica

Supplementum 625

## The Ustaoset Hypertension Meeting 1978

Report from the 8th Nordic Hypertension Meeting  
in Ustaoset, Norway April 13-14 1978

Edited by Per Lund-Johansen



# **The Ustaoset Hypertension Meeting 1978**

**Report from the 9th Nordic Hypertension Meeting  
In Ustaoset, Norway April 13-14 1978**

**Edited by Per Lund-Johansen**



# Acta Medica Scandinavica

originally published as *Nordiskt Medicinskt Arkiv* was founded in 1869 by Professor Axel Key MD. In 1901 (from volume 34) this journal was divided into a medical and a surgical section. Since 1919 (from volume 52) the medical section has been published under the name of *Acta Medica Scandinavica*.

## *Acta Medica Scandinavica*

publishes papers on general medicine mainly from Denmark, Finland, Iceland, Norway, Sweden and the Netherlands. Short preliminary reports (not exceeding two pages) will be published at short notice. The papers are published in English, French or German. *Acta Medica Scandinavica* is published on a non profit basis.

## *Subscriptions*

to *Acta Medica Scandinavica* (two volumes of six numbers each annually) include free supplements to the current volumes.

## *Subscription Rates*

Per annum = two volumes

In Denmark, Finland, Iceland, Norway, Sweden and the Netherlands: Sw. cr. 300 incl. postage. Swedish subscribers add VAT.

Other countries: Sw. cr. 345 incl. postage.

## *Chief Editor*

Professor Jan G. Waldenström, MD  
*Acta Medica Scandinavica*  
Kungsgatan 54  
S-111 35 Stockholm, Sweden

## *Editorial Office*

*Acta Medica Scandinavica*  
Kungsgatan 54  
S-111 35 Stockholm, Sweden  
(All correspondence concerning manuscripts and editorial matters)  
Telephone 08/21 77 63

## *Subscription, Distribution and Advertising*

The Almqvist & Wiksell Periodical Company  
Gamla Brogatan 26, Box 62  
S-101 20 Stockholm 1, Sweden

## *Printers*

Almqvist & Wiksell Tryckeri AB  
S-751 81 Uppsala, Sweden

# **The Ustaoset Hypertension Meeting 1978**

**Report from the 9th Nordic Hypertension Meeting  
in Ustaoset, Norway April 13-14 1978**

**Edited by Per Lund-Johansen**

# Acta Medica Scandinavica

originally published as *Nordiskt Medicinskt Arkiv* was founded in 1869 by Professor Axel Key MD In 1901 (from volume 34) this journal was divided into a medical and a surgical section Since 1919 (from volume 52) the medical section has been published under the name of *Acta Medica Scandinavica*

## *Acta Medica Scandinavica*

publishes papers on general medicine mainly from Denmark Finland, Iceland Norway Sweden and the Netherlands. Short preliminary reports (not exceeding two pages) will be published at short notice. The papers are published in English French or German *Acta Medica Scandinavica* is published on a non profit basis

## *Subscriptions*

to *Acta Medica Scandinavica* (two volumes of six numbers each annually) include free supplements to the current volumes

## *Subscription Rates*

Per annum = two volumes.

In Denmark Finland, Iceland, Norway Sweden and the Netherlands Sw cr 300 incl postage Swedish subscribers add VAT

Other countries Sw cr 345 incl postage

## *Chief Editor*

Professor Jan G Waldenström MD  
*Acta Medica Scandinavica*  
Kungsgatan 54  
S-111 35 Stockholm Sweden

## *Editorial Office*

*Acta Medica Scandinavica*  
Kungsgatan 54  
S-111 35 Stockholm Sweden  
(All correspondence concerning manuscripts and editorial matters)  
Telephone 08/21 77 63

## *Subscription Distribution and Advertising*

The Almqvist & Wiksell Periodical Company  
Gamla Brogatan 26, Box 62  
S-101 20 Stockholm 1 Sweden

## *Printers*

Almqvist & Wiksell Tryckeri AB  
S-751 81 Uppsala Sweden

# CONTENTS

Introduction	5
■ Ohlsson H C Henningsen Hemodynamic investigations on relatives of patients with essential hypertension	7
L Andrén L Hansson M Björkman A Jonsson K O Borg Hemodynamic and hormonal changes induced by noise	13
■ Andersson L Hansson R Sivertsson: Primary hypertension refractory to triple drug treatment - a study on central and peripheral hemodynamics	19
B Harvald J Fabricius A Thomsen Haemodynamic parameters in hypertensive patients treated with a diuretic and with a diuretic in combination with a beta blocker	22
T Lysbo Svendsen J Trap-Jensen J Bliddal O Hartling A McWair Acute hemodynamic effects of five beta-adrenoceptor blocking agents in man the significance of selectivity and intrinsic sympathomimetic activity	26
S Ljungman M Hartford M Aurell G Berglund: Pathophysiological mechanisms of the antihypertensive effect of a cardioselective beta-adrenoceptor blocking drug (metoprolol)	31
B Ljung B Åblad E Almgren C-G Dahlöf B-M Eriksson: Effects of metoprolol on adrenergic mechanisms during long- and short-term antihypertensive treatment of spontaneously hypertensive rats	36
■ Thulesius Beta-adrenergic blockade and vasospasm	41
E Åström A Juhlin-Dannfelt Effect of beta-blockade on leg blood flow and lactate release in exercising man	44
T Lysbo Svendsen S Rasmussen P E Nielsen O Hartling J Trap-Jensen Hemodynamic effects of acute and long-term treatment with labetalol	49
P Lund-Johansen Hemodynamic long-term effects of labetalol in essential hypertension	54
H J Kornerup E E Pedersen M J Christensen A Pedersen E Pedersen Labetalol in the treatment of severe essential hypertension Relationship between arterial blood pressure plasma catecholamines plasma renin activity plasma aldosterone and body weight	59
O Lederhelle Pedersen E Mikkelsen H J Kornerup M J Christensen Effects of nifedipine on blood pressure regional hemodynamics Plasma renin activity and plasma catecholamines in patients with arterial hypertension	65
M Frisk-Holmberg L Paalzow: Relationship between clonidine kinetics and its blood pressure effects	69



# CONTENTS

Introduction	5
O Ohlsson H C Henningsen: Hemodynamic investigations on relatives of patients with essential hypertension	7
L Andr�n L Hansson M Bj�rkman A Jonsson K � Borg: Hemodynamic and hormonal changes induced by noise	13
O Andersson L Hansson R Sivertsson Primary hypertension refractory to triple drug treatment - a study on central and peripheral hemodynamics	19
B Harvald J Fabricius A Thomsen: Hemodynamic parameters in hypertensive patients treated with a diuretic and with a diuretic in combination with a beta-blocker	22
T Lysbo Svendsen J Trap-Jensen J Bliddal O Hartling A McHair Acute hemodynamic effects of five beta-adrenoceptor blocking agents in man: the significance of selectivity and intrinsic sympathomimetic activity	26
� Ljungman M Hartford M Aurell G Berglund: Pathophysiological mechanisms of the antihypertensive effect of a cardioselective beta-adrenoceptor blocking drug (metoprolol)	31
B Ljung B �blad O Almgren C-G Dahl�f B-M Eriksson Effects of metoprolol on adrenergic mechanisms during long- and short-term antihypertensive treatment of spontaneously hypertensive rats	36
� Thuleius Beta-adrenergic blockade and vaso pasm	41
H �str�m A Juhlin-Dannfelt Effect of beta blockade on leg blood flow and lactate release in exercising man	44
T Lysbo Svendsen S Rasmussen P E Nielsen O Hartling J Trap-Jensen Hemodynamic effects of acute and long-term treatment with labetalol	49
� Lund-Johansen Hemodynamic long-term effects of labetalol in essential hypertension	54
H J Kornerup E B Pedersen M J Christensen A Pedersen H Pedersen Labetalol in the treatment of severe essential hypertension Relationship between arterial blood pressure plasma catecholamines plasma renin activity plasma aldosterone and body weight	59
� Lederballe Pedersen E Mikkelsen H J Kornerup M J Christensen Effects of nifedipine on blood pressure regional hemodynamics Plasma renin activity and plasma catecholamines in patients with arterial hypertension	63
M Friisk-Holmberg L Palzow: Relationship between clonidine kinetics and its blood pressure effects	68

- J Tuomilehto A Nissinen A comparison between metoprolol  
alprenolol and oxprenolol in the treatment of hypertension
- I Paakkari H Karppanen P Paakkari: Histaminergic and  
related mechanisms in the central control of blood pressure
- T Gudbrandsson L Hansson Combination therapy with  
saluretics and atenolol in essential hypertension Effects  
on blood pressure electrolytes and uric acid
- P E Nielsen T Hilden Intra-arterial blood pressure  
measured during 24-hours in evaluation of hypertensive  
subjects
- H Ibsen A Leth M Hollnagel A M Kappelgaard M Damkjær  
Nielsen N J Christensen J Giese Renin angiotensin  
system and sympathetic nerve activity in mild essential  
hypertension The functional significance of angiotensin II  
in untreated and thiazide treated hypertensive patients
- E B Pedersen H J Kornerup: Effect of sodium loading on  
the renin-aldosterone system in essential hypertension
- L Mørkrid B M Iversen J Ofstad: Afferent arteriolar  
diameter in DOCA-hypertensive and post-DOCA hypertensive  
rats estimated by means of microspheres
- H Herlitz S Lundin S-E Ricksten G Göthberg M Aurell  
M Hallbäck G Berglund: Sodium balance and structural  
vascular changes in the kidney during development of  
hypertension in spontaneously hypertensive rats
- R Sivertsson E Hansson B Eriksson: Hemodynamic signs  
indicating structural vascular changes of hypertensive type  
after surgery for aortic coarctation
- C Mörlin L-E Löfrelius P-O Löfroth L Wide L Wiklund  
H Åberg: The effect of splanchnic block on renal haemodynamics  
and renin production in hypertensive patients
- M Rajasalmi O Oilinki J Takkunen: The effect of  
hypertension on the mechanocardiographic and electro-  
cardiographic measurements
- A Helgeland P Leren S C Enger I Hjermann I Holme:  
HDL-cholesterol in antihypertensive treatment The Oslo  
study
- I Nielsen B Hesse P Christensen On the pathogenetic  
role of prostaglandins in Bartter's syndrome
- P Fauchald A Helgeland: Treatment of hypertension with  
Prazosin An open study in general practice

## INTRODUCTION

This symposium represents the 9th in a series of meetings between hypertension researchers in the Nordic countries Denmark Finland Norway and Sweden. At the last meeting in 1976 it was decided to publish the abstracts from these meetings and the first report appeared in Acta Medica Scandinavica Supplement 602, 1976 edited by Lennart Hansson Sweden. The great interest in reprints from this volume have convinced the organizers that also the abstracts from the following meetings should be published. This is the second report in this series.

The Organizing Committee (Denmark: Jørn Giese Tage Hilden Hans Ibsen; Finland: Antti Eisalo Pentti Halonen Heikki Karppanen; Norway: Harald Aars Per Lund Johansen Haakon Storm Mathisen; Sweden: Lennart Hansson Bertil Hood Bengt E Karlberg) wishes to express its gratitude to the Scandinavian division of Merck Sharp & Dohme who through a generous grant made this meeting and the printing of this volume possible. We would also particularly thank MSD Norge A/S by director Per Wold Olsen and Mrs. Ellen Wright Kristoffersen for invaluable technical and secretarial aid.

Per Lund Johansen  
Medical Department A  
University of Bergen  
School of Medicine  
5016 Haukeland Hospital  
Bergen  
Norway





# HEMODYNAMIC INVESTIGATIONS ON RELATIVES OF PATIENTS WITH ESSENTIAL HYPERTENSION

B Ohlsson M C Henningsen

Department of Medicine and Clinical physiology Malmö General  
Hospital Sweden

Many attempts have been made to find early hemodynamic changes  
in patients with essential hypertension. The basis of these studies  
has mostly been patients with borderline or labile hypertension  
(1 2 3 4 5 6 7 8)

Our basis has been genetic. By examining relatives of patients with  
essential hypertension we have had possibility to study the problem in  
very early stage

## MATERIAL:

The material consists of 76 patients with essential hypertension who  
were treated at the hospital. They all had informed us that at least  
one person in the last two generations had suffered from the disease.  
Hypertension was also caused to exist in family members suffering  
from cerebrovascular incidents before the age of 60 years. Presence  
of diabetes or secondary hypertension mechanisms like renal artery  
stenosis was disqualifying for this study.

From the 76 persons we received anamnestic data about 801 relatives.  
We were informed that about 50 % of these relatives probably had suffered  
from essential hypertension or sequelae of this disease.

The relatives who were still alive and had no known hypertension were  
called to hospital for examination. 255 relatives were accounted for in  
this study. 31 of these relatives have been examined with invasive  
hemodynamic investigations including continuous blood pressure registra-  
tion and determination of cardiac output during various provocation tests.  
17 volunteers without known hypertension in their families have been  
used as a control group.

53 relatives and 25 controls have been investigated in regard to  
plasma volume at rest.



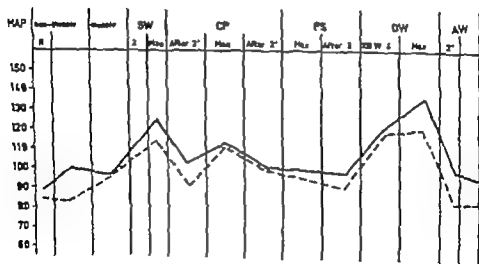
	N	DBP	HR	CI	PRI
Relatives	31	78.8	68	3.3	30.8
Controls	19	74.0	69	3.6	28.1

(Number DBP Diastolic blood pressure HR Heart rate  
CI Cardiac index PRI peripheral resistance index)

The peripheral resistance is about 9 % higher in the relative group. Subdividing the group into the ages 20-30, 30-40 and over 40 one can find that in the latter age group there are five persons who have a lower cardiac output and consequently a higher peripheral resistance than their controls despite a diastolic blood pressure which is identical with that of their controls.

As a whole there are no differences between the relatives and the control in regard to the maximal blood pressure during the provocative tests. Relatives in the oldest age group however do differ from their control in this parameter.

(Fig. 1)



41 56 years  
Relatives ——— n 13  
Controls - - - - n 8

(R rest P pain SW static work CP cold pressure PS psychical stress DW dynamic work AW after work)

## METHODS:

All blood pressures were measured by the same nurses. The patients rested in supine position for 10 minutes before the reading. Korotkoff sound phase 5 was used for determination of the diastolic pressure. The blood pressure was measured in both arms, the higher then recorded for this investigation.

The invasive investigations were performed at the dept. of Clin. Physiol. The patients came after fasting to the laboratory in the morning. A catheter (PE-160) was inserted percutaneously to the right atrium under x-ray control. Another catheter of the same size was inserted in the brachial artery after previous anesthesia. The tip of the catheter was placed in the axillary region. The cardiac output was determined with the dye dilution technique using bromsulphthalein as indicator substance. Plasmavolume was determined by Evans blue after 15 minutes equilibration. The central plasmavolume was calculated from the dye dilution curves using the formula: mean transit time (MTT) x cardiac output (CO) (ref. 9). The peripheral resistance was calculated by dividing mean arterial pressure (MAP) by CO. During continuous intraarterial blood-pressure registration the following provocation tests were performed: pain stimulus during insertion of the catheter into the antecubital vein; static muscle work at 30 % of the individual maximal capacity during five minutes; cold pressure test during 2 minutes; psychical stress with a binary choice generator and dynamic work up to maximal capacity. All tests were performed with the patient in supine position. Cardiac output was determined in the middle of all the above tests excluding pain-stimulus. During dynamic work with a ergometer cycle we determined cardiac output after 2 minutes at 50 and 150 Watt.

## RESULTS

We chose to use the Humerfeldt study of the inhabitants of Bergen (10) as a reference for expected blood pressures in various age groups. We found that 65 % of our relatives have a blood pressure which is higher than expected for their age.

It was decided that one normotensive member of each family should undergo the invasive examination. As a control group we used an age and weight matched group without known hypertension in their families. Table 1 shows the basal data in the two groups:

pressure and high peripheral resistance. In our material the plasma volume is lower without correlation to diastolic blood pressure or peripheral resistance.

The explanation of these results can only be speculative. One hypothesis is that the relatives have high sympathetic tone with subsequent constriction in the postcapillary venules and in the venous reservoirs. The lower plasma volume could be an adaptation to the restriction of these vessels. Preliminary data from our investigations (21) on the sodium metabolism of the relatives shows an elevated intracellular sodium metabolism which could result in increased sensitivity to catecholamines (22). It is also possible that the normotensive relatives have already begun to acquire arterial lesions causing increased sensitivity in the kidneys volume receptors. Lastly, the relatives could have occasional blood pressure level ones with a high transcapillary escape.

Other authors have found circulatory alterations in early and persistent hypertensive individuals. Our data from an hereditarily prone material consisting of relatives of hypertensive patient testify to the existence of circulatory alterations even in normotensive condition. These results motivate further genetic-oriented investigations of hypertensive families in order to better define hemodynamic and metabolic changes in the earlier stages of hypertension.

#### REFERENCES

1. Bell C T, Sevy R W & Harskel C. Varying hemodynamic patterns in essential hypertension. *Am J Med Sci* 250:58 1965.
2. Eich R H, Peters R J, Cuddy R P, Smulyan H & Lyons R K. The hemodynamics in labile hypertension. *Am Heart J* 63:188 1962.
3. Finkelstein S, Morcel M & Agrest A. Hemodynamic patterns in essential hypertension. *Circulation* 31:356 1965.
4. Frohlich E D, Kozul V J, Trezi R C & Dustan H P. Physiological comparison of labile and essential hypertension. *Circ Res* 37 suppl 1:55 1970.
5. Julius S & Conway J. Hemodynamic studies in patients with borderline blood pressure elevation. *Circulation* 38:282 1968.
6. Lund-Johansen P. Hemodynamics in early essential hypertension. *Acta Med Scand* 183 suppl 402 1968.
7. Carey R, Ayers C. Labile hypertension: Precursor of sustained essential hypertension. *The Am J Med* 61:811 1976.

The total plasma volume and hematocrit of 53 relatives and 25 controls was also calculated. Although the hematocrit was the same in both groups the relatives as a whole had a significantly lower ( $p < 0.001^*$ ) plasma volume than their controls: 15.1 versus 19.0 ml/cm height. The difference was accentuated in the 20-30 age group where the plasma volumes were 15.6 versus 19.8 ml/cm. The mean diastolic blood pressure for this age group was 80 mm Hg for the relatives and 75 mm Hg for their controls. The mean for the entire material was a little higher: relatives 83 mm Hg versus controls 78 mm Hg.

## DISCUSSION

There seems to exist some hemodynamic differences between normotensive relatives in hypertension prone families and a control group without known hypertension in their families. In this study we have found significant differences in regard to total plasma volume between the two groups. There is also a tendency to a higher central shift of the plasma volume during dynamic muscle work. A subgroup of the relatives show a higher blood-pressure response during muscle work.

Follow up studies of persons with borderline and labile hypertension present very diverging results ranging from no higher risk of disease manifestation to double the risk. Our anamnestic data shows that eventually persistent hypertension appears in about 50 % of the families. Contrary to several studies in borderline hypertension (2, 3, 4, 5, 6, 7) we have not found any signs of hyperkinetic circulation. Conceivable mechanisms behind the high cardiac output sometimes found in borderline hypertension data include a primary disturbance in the myocardium (11), vagal inhibition (12) and sympathetic hyperactivity. One hypothesis is that sympathetic hyperactivity could cause a diminished capacitance volume with increased central plasma volume and cardiac output.

Safar (13), Tarazi (14), Ulrych (15) find higher central plasma volume in patients with borderline and persistent hypertension. The correlation exists however only during simultaneous presence of high cardiac output. Other authors have found lower plasma volume in hypertensives (16, 17, 18, 19, 20). The referred materials are inhomogenous consisting of all stages of hypertension including borderline and persistent hypertension. In some borderline groups one has not only found a significantly lower plasma volume in comparison to a normotensive control group but also a correlation between lower plasma volume and a slightly higher diastolic blood

# HEMODYNAMIC AND HORMONAL CHANGES INDUCED BY NOISE

Lennart Andrén    Lennart Hult    Martin Björkman

Anders Jönsson and Karl-Olof Borg

From the Department of Medicine, Uster Hospital  
Institut of Occupational Medicine, Sahlgrenska Hospital  
Department of Hygiene, University of Göteborg and  
Hälsö AB, Göteborg, Sweden

**Abstract** Eighteen healthy male volunteers with normal hearing were exposed to industrial noise at different sound levels (75 dB and 95 dB A) in a noise laboratory. Blood pressure, heart rate, stroke volume and cardiac output were recorded with non-invasive techniques. Adrenaline and noreadrenaline concentration in venous plasma were analyzed before and during noise exposure. The mean resting blood pressure of the whole group was 120/70 mm Hg. During noise stimulation diastolic blood pressure increased (12.2%,  $p < 0.001$ ) as did mean arterial pressure (6.6%,  $p < 0.001$ ) and total peripheral resistance (12.7%,  $p < 0.001$ ). Stroke volume (7.3%,  $p < 0.001$ ) and cardiac output (5.0%,  $p < 0.01$ ) were both reduced at 95 dB A.

Heart rate and systolic blood pressure did not change significantly. At 75 and 85 dB A there were smaller but smaller changes in the hemodynamic parameters.

There were no changes in adrenaline and noreadrenaline in plasma during maximal noise exposure.

The noise induced hemodynamic changes remained 5 minutes after the noise stimulation was stopped but had disappeared after 10 minutes of rest.



- 8 Sannerstedt R Sivertsson R Lundgren Y : Hemodynamic studies in young men with mild blood pressure elevation Acta Med Scand suppl 602:61 1976
- 9 Yang S Bentivoglio L Maranhao V Goldberg H : From Cardiac catheterization data to hemodynamic parameters F A Davis Company Philadelphia 1972
- 10 Bbe J Humerfelt S Wedervang F : The blood pressure in a population Acta Med Scand Suppl 321 1957
- 11 Levy A M Tabakin B S Hanson J S : Hemodynamic responses to graded treadmill exercise in young untreated labile hypertensive patients
- 12 Julius S Pascual A London R Role of parasympathetic inhibition in the hyperkinetic type of borderline hypertension Circulation vol 44 1971
- 13 Safar M E Weiss G M London R Frachowiak R F Milliez P L Cardiopulmonary blood volume in borderline hypertension Clin Sci Mol Med 47:153 1974
- 14 Tarazi R C Ibrahim M Dustan H Ferrario C : Cardiac factors in hypertension Circulation Res 34 35 suppl 1 213
- 15 Ulrych M Frohlich E Tarazi R Dustan H Page I: Cardiac output and distribution of blood volume in central and peripheral circulation in hypertensive and normotensive man Brit Heart J 31 570 1969
- 16 Tarazi R Dustan H Frohlich E: Relation of plasma to interstitial fluid volume in essential hypertension Circulation vol 40 1969
- 17 Tarazi R Dustan H Frohlich E: Plasma volume and chronic hypertension Arch Intern Med vol 125 1970
- 18 Ibsen H Leth A Plasma volume and extracellular fluid volume in essential hypertension Acta Med Scand vol 194 1973
- 19 Ulrych M : Plasma volume decrease and elevated Evans blue disappearance rate in essential hypertension Clin Sci and Mol Med 45:173 1973
- 20 Julius S Pascual A Reilly K London R : Abnormalities of plasma volume in borderline hypertension Arch Intern Med 127 1971
- 21 Henningsen N C Noselin B Mattson S Ohlsson H : Publication under preparation
- 22 De Champlain J Krakoff L & Axelrod J : Relation between sodium intake and norepinephrine storage during the development of experimental hypertension Circ Res 23:479 1968

# HEMODYNAMIC AND HORMONAL CHANGES INDUCED BY NOISE

Lennart Andrén Lennart H     e     Martin Björkman  
Anders Jonsson     nd Karl Olof     rg

From the Department of Medicine     Östra Hospital  
Institute of Occupational Medicine     Sahlgrenska Hospital  
Department of Hygiene     University of Göteborg     nd  
H     AB Göteborg     Sweden

**Abstract** Eighteen healthy male volunteers with normal hearing were exposed to industrial noise at different sound levels (75, 85 and 95 dB A) in a noise laboratory. Blood pressure, heart rate, stroke volume and cardiac output were recorded with non-invasive techniques. Adrenaline and noreadrenaline concentration in venous plasma were analyzed before and during noise exposure. The mean resting blood pressure of the whole group was 120/70 mm Hg. During noise stimulation diastolic blood pressure increased (12.2%,  $p < 0.001$ ) as did mean arterial pressure (6.6%,  $p < 0.001$ ) and total peripheral resistance (12.7%,  $p < 0.001$ ). Stroke volume (7.3%,  $p < 0.001$ ) and cardiac output (5.0%,  $p < 0.01$ ) were both reduced at 95 dB A. Heart rate and systolic blood pressure did not change significantly. At 75 and 85 dB A there were small but smaller changes in the hemodynamic parameters. There were no changes in adrenaline and noreadrenaline in plasma during maximal noise exposure. The noise induced hemodynamic changes remained 5 minutes after the noise stimulation was stopped but had disappeared after 10 minutes of rest.

It has been known for several decades that noise can cause temporary blood pressure increments in animals e g different strains of rats. In 1948 Yeakel et al (1) showed that daily noise exposure to rats for several months resulted in a blood pressure increase which remained for four months after the noise stimulation had stopped. Furthermore they showed that if the animal was reexposed to noise the blood pressure increment came faster than during the initial exposure indicating a mechanism of sensitization in the animal.

Several studies have shown that different stress stimuli e g noise can produce temporary blood pressure increments in SHR-rats and that these stimuli accelerate the development of permanent hypertension (2-4-7). Jonsson and Hansson have shown that industrial workers with a severe noise induced hearing impairment (defined as more than 65 dB A hearing loss at the frequencies 3000, 4000 or 6000 Hz) had significantly higher blood pressure compared to an age-matched control group with normal hearing (defined as less than 20 dB hearing loss at any frequency); 8. Furthermore in the group with noise induced hearing loss there were significantly more hypertensives compared with the control group (8). This made us interested in further evaluations of the effect of noise on blood pressure and other hemodynamic variables. Thus the aim of the present study was to investigate the hemodynamic and hormonal effects of acute noise stimulation in man.

#### PATIENTS AND METHODS

Eighteen male healthy volunteers with normal hearing (audiometry) participated in the investigation. Their mean age was 26 years, range 23-31. They were studied in the afternoon under strictly standardized conditions in a noise laboratory. Following 20 minutes rest in the supine position at a sound level of 40 dB A noise stimulation started. The patients were divided into two groups. The first group (n 8) was exposed to increasing noise levels in 10 minute periods starting with 75 dB A followed by 85 dB A and 95 dB A. The other group (n 10) was exposed directly to 95 dB A for 20

with sound levels up to 105 dB A. The hemodynamic parameters were recorded several times before and after the noise stimulation. Adrenaline and noradrenaline in venous plasma were studied after 20 minutes rest in the supine position and after 5 minutes of noise exposure at 95 dB A. The subjective experience of the noise disturbance was registered in a questionnaire. The investigation was ended by resting period at 40 dB A.

Blood pressure was measured indirectly with a sphygmomanometric blood pressure recorder (Boech B 60 at). There was a very good correlation ( $r = 0.93$ ,  $p < 0.001$ ) between simultaneously recorded blood pressure with a mercury manometer and the sphygmomanometric blood pressure recorder. Diastolic blood pressure was measured with the disappearance of the Korotkoff sounds (phase V). Heart rate and stroke volume were recorded noninvasively with impedance cardiography (9). Its correlation with dye dilution technique (Cardio Green) was  $r = 0.89$ ,  $p < 0.001$  (13). It is known to be at least as reliable as the dye dilution technique as essential changes in stroke volume in the same period (10, 12).

Total peripheral resistance was calculated as the quotient of mean arterial blood pressure and cardiac output. The blood samples for catecholamine analysis (13) were taken from a cannula inserted in the antecubital vein 10 minutes before the test period at rest.

## RESULTS

At 95 dB A there were highly significant increases in diastolic blood pressure (12.2%,  $p < 0.001$ ), mean arterial pressure (6.6%,  $p < 0.001$ ) and total peripheral resistance (12.7%,  $p < 0.001$ ); Fig. 1.

The stroke volume decreased significantly (7.3%,  $p < 0.001$ ) and the cardiac output (5.0%,  $p < 0.01$ ). Heart rate and systolic blood pressure did not change significantly.

At 75 dB A there were statistically significant increases in diastolic blood pressure (5.0%,  $p < 0.05$ ), mean arterial pressure (3.2%,  $p < 0.05$ ) and total peripheral resistance

It has been known for several decades that noise can cause temporary blood pressure increments in animals e g different strains of rats In 1948 Yeakel et al (1) showed that daily noise exposure to rats for several months resulted in a blood pressure increase which remained for four months after the noise stimulation had stopped Furthermore they showed that if the animal was reexposed to noise the blood pressure increment came faster than during the initial exposure indicating a mechanism of sensitization in the animal

Several studies have shown that different stress stimuli e g noise can produce temporary blood pressure increments in SHR-rats and that these stimuli accelerate the development of permanent hypertension (2 4-7) Jonsson and Hansson have shown that industrial workers with a severe noise induced hearing impairment (defined as more than 65 dB A hearing loss at the frequencies 3000 4000 or 6000 HZ) had significantly higher blood pressure compared to an age-matched control group with normal hearing (defined as less than 20 dB hearing loss at any frequency); 8 Furthermore in the group with noise induced hearing loss there were significantly more hypertensives compared with the control group (8) This made us interested in further evaluations of the effect of noise on blood pressure and other hemodynamic variables Thus the aim of the present study was to investigate the hemodynamic and hormonal effects of acute noise stimulation in man

#### PATIENTS AND METHODS

Eighteen male healthy volunteers with normal hearing (audiometry) participated in the investigation Their mean age was 26 years range 23 31 They were studied in the afternoon under strictly standardized conditions in a noise laboratory Following 20 minutes rest in the supine position at a sound level of 40 dB A noise stimulation started The patients were divided into two groups The first group (n 8) was exposed to increasing noise levels in 10 minute periods starting with 75 dB A followed by 85 dB A and 95 dB A The other group (n 10) was exposed directly to 95 dB A for 20 minutes There were also intermittent brief sound disturbances

disturbance and objectively recorded hemodynamic changes

The hemodynamic changes were still present 5 minutes after the noise stimulation was stopped but they had disappeared after 10 minutes of quiet rest at 40 dB A

There were no significant changes in adrenaline or adrenaline concentration in plasma during maximal noise stimulation (95 dB A) nor were there any correlation between the change in hemodynamic parameters and the catecholamine concentrations

### DISCUSSION

Acute noise exposure caused temporary blood pressure increase in normal volunteers. The blood pressure increase was associated with increased to use in the resistance vessels dictated by the peripheral resistance. This was reversible when the noise stimulation was stopped. The decrease in stroke volume and cardiac output could be secondary to the peripheral resistance. We did not find a linear relationship between noise level and blood pressure increase and all hemodynamic changes with the exception of the regarding stroke volume and cardiac output were pronounced at 85 dB A compared with 75 dB A

There could be several different reasons for the abrupt change in sound level from the very quiet 40 dB A to 75 dB A is proportionally great increase in noise level the change from 75 dB A to 85 dB A

Another possible explanation could be that the total hemodynamic changes at 75 dB A might be secondary to combination of the noise exposure and perceptual stress

There are different opinions regarding chronic noise exposure and its possible association with permanent hypertension in man (8, 14, 15)

Several factors could modify the cardiovascular response to noise in man as well as in animals. Repeated daily noise exposure for long periods would conceivably result in a permanent increase in blood pressure. The relationship between noise and blood pressure is still a controversial issue with findings from animal studies (7)

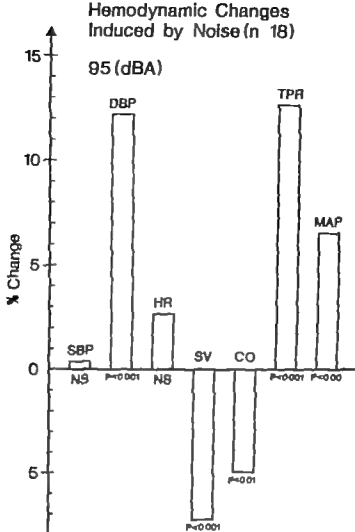


Fig 1 Hemodynamic changes in 18 healthy subjects caused by noise stimulation at 95 dB A

(11.1%  $p < 0.05$ ) Heart rate (3.2% n.s.) stroke volume (3.6% n.s.) systolic blood pressure increased (1.1% n.s.) and cardiac output (6.2% n.s.) did not change significantly

At 85 dB A there were changes similar to those at 75 dB A although they were less pronounced

There were no significant differences at 95 dB A between the group which was exposed to a step wise increase in noise and the group which was directly stimulated with 95 dB A

Loud short intermittent noise (105 dB A) did not accentuate the hemodynamic response elicited by continuous noise at 95 dB A

There was no correlation between subjectively experienced

Primary hypertension refractory to tripl drug treatment a study  
on central and peripheral hemodynamic

by

Ove Andersson M.D. Lennart Hansson M.D. and Ramon Siertson M.D.

Department of Medicine I and Department of Clinical Physiology II  
University of Göteborg Göteborg Sweden

Hemodynamic factors involved in blood pressure regulation were investigated in 20 hypertensive patients refractory to the combined treatment with diuretic (hydrochlorothiazide 50 mg daily or bendroflumethiazide 5 mg daily) propranolol 120-160 mg t.i.d. and hydralazine 50-75 mg t.i.d. The patients were compared with ten other hypertensive patients matched for sex, age, weight, glomerular filtration rate and initial untreated blood pressure responding adequately to the corresponding therapy. On the triplicate the procedure used for more than two years, none of the refractory patients had mean arterial pressure reduction of 10% or more, no were their blood pressure below 200/110 mm Hg at the clinic. The responding patients had reduction of mean arterial pressure of 20% or more and blood pressure below 180/100 mm Hg at the clinic. The patients in each pair had the same drug and doses and they were checked for drug defauling (1) All the twenty patients had high degree of  $\beta$ -adrenoceptor blockade, judged from isoprenaline infusion (1). The ten patients in the refractory group were low acetylators of hydralazine while five of the responders were fast acetylators. The patients in both groups had primary hypertension and 11 had eye-ground changes grade II (K.V.B.). Cardiac output was determined with dye dilution technique (indocyanine green) and plasma volume with Evans blue. Blood flow and vascular resistance at rest and at maximal vasodilatation in a skin (hand) and muscle (calf) vascular bed were determined using venous occlusion plethysmography and 12 arterial and auscultatory blood pressure recordings respectively. Maximal vasodilatation was obtained by direct and indirect heating, a 2 min occlusion and digital work (hand) by 12 min occlusion and muscle work (calf).



# REFERENCES

- 1 Yeaskel E H Shenkin H A Rothballer A B & McDonald McCann S  
Amer J Physiol 155 118 1948
- 2 Rothlin E Corletti A & Emmenegger H  
Acta Med Scand 154 (Suppl 312): 27 1956
- 3 Eriksson M M Andersson I Borg K O & Persson B A  
Acta Pharm Suecica 14: 451 1977
- 4 Folkow B & Rubinstein E H  
Acta Physiol Scand 68: 48 1966
- 5 Hallbäck M & Folkow B  
Acta Physiol Scand 90: 684 1974
- 6 Herd A J Morse W H Kelleher R T & Jones L G  
Amer J Physiol 217: 24 1969
- 7 Hallback M  
Acta Physiol Scand Suppl 424 1975
- 8 Jonsson A & Hansson L  
Lancet ii: 86 1977
- 9 Lorimer A R MacFarlane P W Provan G  
Duffy J & Lawrie T D V  
Cardiovasc Res 5: 169 1971
- 10 Kubicek W G Patterson R P & Witasek D A  
Ann N Y Acad Sci 724 1970
- 11 Judy J Judson D C Grim C E & Weinberger M H  
Clin Res 25: 229 A 1977
- 12 Gabriel S Atterhög J H Orö L & Ekelund L G  
Scand J Clin Lab Invest 36: 1976
- 13 Grønervik G & Elg R  
To be published
- 14 Takala J Varke S Vaheri E & Sievers K  
Lancet ii: 974 1977
- 15 Hedstrand H Drottner B Klockhoff J & Svedberg A  
Lancet ii: 1291 1977

Primary hypertension refractory to triple drug treatment - a study on central and peripheral hemodynamics

by

Ovo Andersson M.D. Lennart Hansson M.D. and Ramon Sivertsson M.D.

Department of Medicine I and Department of Clinical Physiology II  
University of Göteborg Göteborg Sweden

Hemodynamic factors involved in blood pressure regulation were investigated in ten hypertensive patients refractory to the combined treatment with diuretics (hydrochlorothiazide 50 mg daily or bendroflumethiazide 5 mg daily) propranolol 120-160 mg t.i.d. and hydralazine 50-75 mg t.i.d. The patients were compared to ten other hypertensive patients matched for sex, age, weight, glomerular filtration rate and initial untreated blood pressure responding adequately to the corresponding therapy. On the triple therapy described above for more than two years none of the refractory patients had a mean arterial pressure reduction of 10% or more, nor were their blood pressures below 200/110 mm Hg at the clinic. The responding patients had a reduction of mean arterial pressure of 20% or more and blood pressure below 180/100 mm Hg at the clinic. The patients in each pair had the same drugs and doses and they were checked for drug faulting.

(1) All the twenty patients had high degree of  $\beta$ -adrenoreceptor blockade judged from isoprenaline infusion (1). The ten patients in the refractory group were slow acetylators of hydralazine while all of the responders were fast acetylators. The patients in both groups had primary hypertension and all had eye-ground changes grade II (K.V.B.). Cardiac output was determined with dye dilution technique (indocyanine green) and plasma volume with Evans Blue. Blood flow and vascular resistance at rest and maximal vasodilation in the hand and muscle (calf) were determined using various occlusion plethysmography and intra-arterial and auscultatory blood pressure recordings respectively. Maximal vasodilation was obtained by direct and indirect heating, arterial occlusion and digital work (hand) by arterial occlusion and muscle work (calf).

## REFERENCES

- 1 Yeakel E H Shenkin H A Rothballer A B &  
McDonald-McCann S  
Amer J Physiol 155 118 1948
- 2 Rothlin E Cerletti A & Emmenegger H  
Acta Med Scand 154 (Suppl 312) 27 1956
- 3 Eriksson B M Andersson I Borg K M &  
Persson B A  
Acta Pharm Suecica 14 451 1977
- 4 Folkow B & Rubinstein E H  
Acta Physiol Scand 68 48 1966
- 5 Hallbäck M & Folkow B  
Acta Physiol Scand 90 684 1974
- 6 Herd A J Morse W H Kelleher R T & Jones  
L G  
Amer J Physiol 217 24 1969
- 7 Hallbäck M  
Acta Physiol Scand Suppl 424 1975
- 8 Jonsson A & Hansson L  
Lancet ii: 86 1977
- 9 Lorimer A R MacFarlane P W Provan G  
Duffy T & Lawrie T D V  
Cardiovasc Res 5 169 1971
- 10 Kubicek W G Patterson R P & Witsoe D A  
Ann N Y Acad Sci 724 1970
- 11 Judy J Judson D C Grim C E & Weinberger  
M H  
Clin Res 25 229 A 1977
- 12 Gabriel S Atterhög J -H Oro L & Ekelund L G  
Scand J Clin Lab Invest 36 1976
- 13 Granerus G & Elg M  
To be published
- 14 Tekala J Varke S Vaheri E & Sievers K  
Lancet iii: 974 1977
- 15 Hedstrand H Drottner B Klockhoff J &  
Svødberg A  
Lancet ii 1291 1977

Primary hypertension refractory to tripl drug treatment - study  
on central and peripheral hemodynamics

by  
Ove Andersson M.D. Leifert Hasson M.D. and Ramon Sivertsson M.D.

Department of Medicine and Department of Clinical Physiology  
University of Göteborg Göteborg Sweden

Hemodynamic factors involved in blood pressure regulation were investigated in ten hypertensive patients refractory to the combined treatment with diuretics (hydrochlorothiazide 50 mg daily or bendroflumethiazide 5 mg daily) propranolol 120-160 mg t.i.d. and hydralazine 50-75 mg t.i.d. The patients were compared to ten other hypertensive patients matched for sex, age, weight, glomerular filtration rate and initial untreated blood pressure responding adequately to the corresponding therapy. On the triplicate daybed used for more than two years none of the refractory patients had a mean arterial pressure reduction of 10% or more nor was their blood pressure below 200/110 mm Hg at the time. The responding patients had a reduction of mean arterial pressure of 20% or more and blood pressure below 180/100 mm Hg at the time. The patients in each pair had the same drug and doses and they were checked for drug defaulting. (1) All the twenty patients had a high degree of  $\beta$ -adrenoceptor blockade as judged from isoprotrenol infusion. (2) The ten patients in the refractory group were slow acetylators of hydralazine while five of the responders were fast acetylators. The patients in both groups had primary hypertension and all had eye-ground changes grade II (K.V.B.). Cardiac output was determined with dye dilution technique (indocyanine green) and plasma volume with Evans Blue. Blood flow and vascular resistance at rest and at maximal vasodilatation in skin (hand) and muscle (calf) were determined using venous occlusion plethysmography and intra-arterial and auscultatory blood pressure recording respectively. Maximal vasodilatation was obtained by direct and indirect heating of the occlusion and digital work (hand) by rubber ball occlusion and muscle work (calf).

The refractory patients had increased total peripheral resistance in comparison with the responders (Table 1) while cardiac output and plasma volume did not differ between the groups. This suggests that the increased peripheral resistance is the important factor for the sustained blood pressure elevation during the influence of the actual therapy. Furthermore, in comparison with the controls the refractory patients had increased vascular resistance at maximal dilatation (Table 1).

Table 1 Central and peripheral hemodynamics in refractory patients and patients responding to triple drug therapy

	Central hemodynamics			Peripheral hemodynamics			
	MAP mm Hg	CI ml/min m <sup>2</sup>	TPRI U/m <sup>2</sup>	Resistance at max dilatation hand PRU <sub>100</sub>	Resistance at max dilatation calf PRU <sub>100</sub>	Resting tone hand	Resting tone calf
Refractory patients	119	2.72	45.9	3.6	3.9	2.7	14.8
Responding patients	94 <sup>xx</sup>	2.70	35.6 <sup>x</sup>	2.8 <sup>x</sup>	2.9 <sup>x</sup>	2.8	13.5

This indicates a vascular abnormality in this group (2). Since the dilatation procedure abolishes smooth muscle tone in the resistance vessels almost completely, the vascular abnormality is interpreted as a structural change, most likely an adaptive thickening of the vessel wall associated with hypertension (3, 5). The results indicate that this abnormality is more pronounced in the patients refractory to treatment.

The ten patients refractory to therapy were then treated with minoxidil (15-35 mg/day) as the only vasodilating agent with the propranolol dose kept constant and the diuretic therapy kept almost constant (increased in one patient). After the change in therapy all ten patients had a reduction of blood pressure below 170/100 mm Hg at the clinic within two months. The blood pressure reduction was correlated to an increase in resting blood flow. A modest increase in plasma volume was noticed.

No change in the resistance at maximal vasodilation was found. Consequently, no sign of reversibility of the vascular abnormality was demonstrated after two months of blood pressure lowering therapy (4).

### References

1. Andersson O: Management of hypertension. Clinical and hemodynamic studies with special reference to patients refractory to treatment (Thesis) Acta med scand suppl 617 1978
2. Conway J: A vascular abnormality in hypertension. A study of blood flow in the forearm. Circulation 27: 520 1963
3. Folkow B, Glimby G, Thulesius O: Adaptive structural changes of the arterial wall in hypertension and their relation to the control of the peripheral resistance. Acta physiol scand 44: 255 1958
4. Lundgren Y: Regression of structural cardiovascular changes after reversal of experimental renal hypertension in rats. Acta physiol scand 91: 275 1974
5. Sjöström R, Hansson L: Effect of blood pressure reduction on the structural vascular abnormality in skin and muscle vascular beds in human essential hypertension. Clin Sci Mol Med 51: 77 1976

The refractory patients had increased total peripheral resistance in comparison with the responders (Table 1) while cardiac output and plasma volume did not differ between the groups. This suggests that the increased peripheral resistance is the important factor for the sustained blood pressure elevation during the influence of the actual therapy. Furthermore, in comparison with the controls the refractory patients had increased vascular resistance at maximal dilatation (Table 1).

Table 1 Central and peripheral hemodynamics in refractory patients and patients responding to triple drug therapy

	Central hemodynamics			Peripheral hemodynamics			
	MAP mm Hg	CI ml/min m <sup>2</sup>	TPRI U/m <sup>2</sup>	Resistance at max dilatation hand PRU <sub>100</sub>	Resistance at max dilatation calf PRU <sub>100</sub>	Resting tone hand	Resting tone calf
Refractory patients	119	2.72	45.9	3.6	3.9	2.7	14.8
Responding patients	94 <sup>xxx</sup>	2.70	35.6 <sup>x</sup>	2.8 <sup>x</sup>	2.9 <sup>x</sup>	2.8	13.5

This indicates a vascular abnormality in this group (2). Since the dilatation procedure abolishes smooth muscle tone in the resistance vessels almost completely, the vascular abnormality is interpreted as a structural change, most likely an adaptive thickening of the vessel wall associated with hypertension (3, 5). The results indicate that this abnormality is more pronounced in the patients refractory to treatment.

(HOE 118) where blood pressure, cardiac output and peripheral vascular resistance had been monitored during the determination of therapeutically acceptable dosage. We have taken the opportunity of comparing these haemodynamic parameters under a pure diuretic treatment and under a combination of diuretic with beta-blocker in the same patients. The patients were on an average rather young ( $\bar{x}$  = 40 years, range 20-59) 11 with a mild hypertension.

The plan of the assay was as follows:

Placebo 2 weeks - HOE 118 in growing dosages 6 weeks - placebo 2 weeks - Baycaron + Inderal 6 months

Blood pressure and cardiac output have been examined and peripheral vascular resistance calculated one or more times during each period. Average parameters for the placebo period for highest dosage of HOE 118 and for maintenance dosage of Baycaron + Inderal have been compared. Cardiac output was determined by an impedance cardiography method (Kubicek et al 1966, Minnesota Impedance cardiograph, model 304 A). Differences have been evaluated by a Student's t-test for paired comparisons and by a sign test estimating whether the relative numbers of positive and negative differences between treatment periods may be ascribed to chance.

Table I gives the average values of body weight, blood pressure, heart rate, cardiac output and peripheral vascular resistance. All parameters have been determined supine and standing. The blood pressure is significantly lower under HOE 118 than under



HAEMODYNAMIC PARAMETERS IN HYPERTENSIVE PATIENTS  
TREATED WITH A DIURETIC AND WITH A DIURETIC IN  
COMBINATION WITH A BETA-BLOCKER

B. Harvald, J. Fabricius and A. Thomsen

Department of Internal Medicine and Clinical Physiology  
Odense University Hospital · Odense · Denmark

Treatment of mild arterial hypertension with a thiazide diuretic as the only antihypertensive drug is well recognized. In Denmark the majority of hypertensive patients taken care of by their practitioner are treated in this way. In our out-patient department however we have for a couple of years used a combination of a small dosage of mefruside (Baycaran®) with a small dosage of propranolol (Inderal®) in mild hypertension. The most commonly used dosage has been 25 mg of mefruside and 40 mg of propranolol taken together in the morning. Especially in younger patients this treatment has proved satisfactory.

In connection with the perusal in 12 hypertensive patients (9 males, 3 females) of a new loop diuretic related to furosemide

lowering seems primarily to be brought about by a reduced cardiac output whereas no significant differences of the calculated peripheral vascular resistance could be demonstrated. In the standing position the pulse rate is higher for all types of treatment, the pulse amplitude is smaller, the cardiac output is lower, and the peripheral vascular resistance is higher.

The body weight is significantly reduced under HOE 118. This is probably due to dehydration and the weight loss is regained under Baycaron + Inderal.

It may be concluded that under a combined diuretic + beta-blocker regimen with very small dosages of both types of drug a more pronounced blood pressure lowering may be attained without dehydration, without postural hypotension, and with no higher peripheral resistance than under a rather massive diuretic treatment. The combined treatment must therefore be preferred.

#### REFERENCES

1. Kubicek W G, Karnegis J N, Patterson R P, Witsoe D A & Mattson R H : Development and evaluation of an impedance cardiac output system. *Aerospace Med* 37:1208, 1966.

Table 1

Haemodynamic parameters in 12 patients with mild arterial hypertension  
Average values under placebo, diuretic (HOE 118) and combined  
diuretic + beta-blocker (Baycaron + Inderal)

		Placebo		HOE 118		Baycaron + Inderal
		<hr/>		<hr/>		<hr/>
Body weight	kg					
		73.0	$p < 0.001$	71.3	$p < 0.001$	73.5
Blood pressure	mm Hg					
supine		154/110	- -	140/104	- -	132/95
standing		150/115	- -	139/109	- -	133/99
Heart rate	/minute					
supine		69	$p < 0.05$	72	- -	59
standing		74	- -	84	- -	65
Cardiac output	l/min					
supine		7.3	- -	6.3	n.s.	6.7
standing		5.7	- -	5.0	n.s.	4.8
Peripheral vascular resistance	dyn sec cm <sup>-5</sup>					
supine		1591	n.s.	1661	n.s.	1465
standing		1971	n.s.	2071	n.s.	2075

placebo ( $p < 0.001$ ) and furthermore significantly lower under Baycaron + Inderal than under HOE 118 ( $p < 0.001$ ). Heart rate is the highest under HOE 118, by far the lowest under Baycaron + Inderal. Both under HOE 118 and under Baycaron + Inderal the blood pressure

lowering seems primarily to be brought about by a reduced cardiac output whereas no significant differences of the calculated peripheral vascular resistance could be demonstrated. In the standing position the pulse rate is higher for all types of treatment, the pulse amplitude is smaller, the cardiac output is lower, and the peripheral vascular resistance is higher.

The body weight is significantly reduced under HOE 118. This is probably due to dehydration, and the weight loss is regained under Baycaron + Inderal.

It may be concluded that under a combined diuretic + beta blocker regimen with very small dosages of both types of drug a more pronounced blood pressure lowering may be attained without dehydration, without postural hypotension, and with no higher peripheral resistance than under a rather massive diuretic treatment. The combined treatment must therefore be preferred.

#### REFERENCES

1. Kubicek W G, Karnegis J N, Patterson R P, Witsoe D A, & Mathon R II : Development and evaluation of an impedance cardiac output system. *Aerospace Med.* 37: 1208, 1966.

# ACUTE HEMODYNAMIC EFFECTS OF FIVE BETA-ADRENOCEPTOR BLOCKING AGENTS IN MAN. THE SIGNIFICANCE OF SELECTIVITY AND INTRINSIC SYMPATHOMIMETIC ACTIVITY.

Lysbo Svendsen T · Trap-Jensen J · Bliddal J · Hartling O and McNair A.

Department of Clinical Physiology Frederiksberg Hospital and Department of Internal Medicine C Diakonlæsestiftelsen DK-2000 Frederiksberg Denmark.

The beta-adrenoceptor blocking agents used in the clinic can be characterized by properties such as selectivity and partial agonism or intrinsic sympathomimetic activity (I s a ) In man the physiological significance of these properties is not yet clear, although the importance of selectivity is obvious in the treatment of patients with obstructive lung disease The practical implication of I s a has not been established. Beta-adrenoceptor blockers with and without I s a have been proven to be equally effective in the antihypertensive treatment but any advantage or disadvantage of I s a, has not yet been demonstrated in man.

The present study was undertaken in order to compare the quantitative effects of different beta-adrenoceptor blockers on heart rate cardiac output and arterial blood pressure Dose response curves for the central hemodynamic effects of I v administration of Propranolol non-selective without I s a Atenolol selective without I s a, Pindolol non-selective with I s a Practolol selective with a weaker I s a, and a new beta-adrenoceptor blocker not yet in clinical use IC1 89 406 selective with I s a.

## Material and methods.

The study comprised 29 patients (25 men and 4 women) who three to six months earlier have had an acute myocardial infarct The mean age was 54 years ranging from 35 years to 68 years All patients were actively employed None had signs of cardiac failure and none were in diuretic or antihypertensive therapy All patients consented to participate in the study after being informed in details of its nature and purpose

The studies were performed in the morning. The patients having fasted over night. The patients were in the supine position in a silent room with a constant temperature of  $23^{\circ}$  celcius. Talking was avoided throughout the study and the patients were instructed to keep as immobile as possible but not allowed to fall asleep. The tip of a Swan-Ganz thermodilution catheter was placed in the pulmonary artery under fluoroscopic guidance. After one hour of supine rest control values for cardiac output (CO), systemic blood pressure (BP), heart rate (HR) and pulmonary artery pressure (PAP) were obtained in duplicate. The CO values used in the following were mean value of five consecutive determinations done within two or three min using an Edwards cardiac output computer. Thereafter with 15 min interval six doses of one of the beta-adrenoceptor blocking agents was administered i.v. in equipotent logarithmic incremental doses. Twelve to 15 min after each injection the above mentioned variables were recorded. In each group the total cumulative dose after the sixth injection of the respective drugs was: Propranolol 0.18 mg/kg b.w. n = 5, At enolol 0.18 mg/kg b.w. n = 6, Pindolol 0.023 mg/kg b.w. n = 6, Practolol 0.64 mg/kg b.w. n = 5, ICI 89 406 mg/kg b.w. n = 7.

### Results:

The dose response curves for HR and CO expressed as per cent change from the control values are shown in Fig 1. The curves fall into three groups according to the degree of effect: a) the curves for pindolol and ICI 89 406 which do not differ significantly from control values, b) the curve for practolol which differs significantly from group a as well as group b, and c) the curves for propranolol and atenolol. It is seen that the last two drugs caused the most pronounced decrease in HR and CO. The BP was essentially unchanged in all patients after the sixth dose. Thus the total peripheral vascular resistance was unchanged after pindolol and ICI 89 406, moderately increased after practolol and markedly increased after propranolol and atenolol.

The mean PAP was significantly increased by three to five mm Hg after propranolol and atenolol but essentially unchanged after practolol, pindolol and ICI 89 406.

# ACUTE HEMODYNAMIC EFFECTS OF FIVE BETA-ADRENOCEPTOR BLOCKING AGENTS IN MAN. THE SIGNIFICANCE OF SELECTIVITY AND INTRINSIC SYMPATHOMIMETIC ACTIVITY.

Lysbo Svendsen T Trap-Jensen, J Bliddal J Hartling O and McNair A.

Department of Clinical Physiology Frederiksberg Hospital and Department of Internal Medicine C Diakonissestiftelsen DK-2000 Frederiksberg Denmark.

The beta-adrenoceptor blocking agents used in the clinic can be characterized by properties such as selectivity and partial agonism or intrinsic sympathomimetic activity (I s a). In man the physiological significance of these properties is not yet clear although the importance of selectivity is obvious in the treatment of patients with obstructive lung disease. The practical implication of I s a has not been established. Beta-adrenoceptor blockers with and without I s a have been proven to be equally effective in the antihypertensive treatment, but any advantage or disadvantage of I s a has not yet been demonstrated in man.

The present study was undertaken in order to compare the quantitative effects of different beta-adrenoceptor blockers on heart rate, cardiac output and arterial blood pressure. Dose response curves for the central hemodynamic effects of I v administration of Propranolol non-selective without I s a, Atenolol selective without I s a, Pindolol non-selective with I s a, Practolol selective with a weaker I s a, and a new beta-adrenoceptor blocker not yet in clinical use ICI 89 406 selective with I s a.

## Material and methods.

The study comprised 29 patients (25 men and 4 women) who three to six months earlier have had an acute myocardial infarct. The mean age was 54 years ranging from 35 years to 68 years. All patients were actively employed. None had signs of cardiac failure and none were in diuretic or antihypertensive therapy. All patients consented to participate in the study after being informed in details of its nature and purpose.

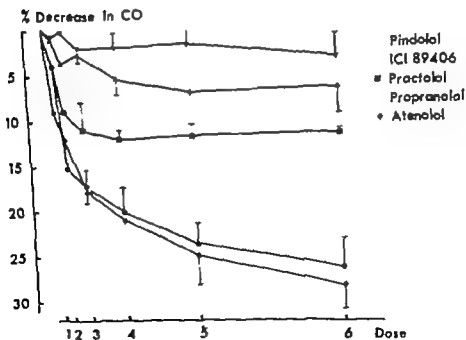
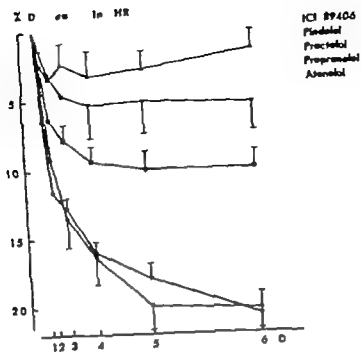


Fig 1 Dose response curves for heart rate (HR) and cardiac output (CO) after i.v. administration of six equipotent logarithmic incremental doses of the beta<sub>1</sub>-adrenoceptor blocking agents to resting men. Mean values +



## Discussion

The present results do not agree with previous results from animal experiments. In anaesthetized dogs acute i.v. administration of practolol up to 4 mg/kg b.w. had only little effect on the aortic flow. Propranolol and atenolol at the same dose level exerted a progressive depressant action with 50 per cent and 30 per cent reduction respectively (2). However, the total cumulative doses in the animal experiments were 20 times higher than the doses used in our study. I.e. unrealistically high for clinical use. The depressant action of propranolol did not differ from that of atenolol up to a cumulative dose of 0.25 mg/kg i.e. within the dose range used here. Therefore we find it justified to conclude that the acute hemodynamic effects of non-selective and selective beta-adrenoceptor blocking agents do not differ significantly from one another within the dose ranges used normally in man.

Do these acute results apply also to long-term treatment with beta-adrenoceptor blockers? With respect to the decrease in HR and CO the long-term effects of propranolol and atenolol seem to be identical to the acute effects here found (3, 4, 5, 6, 7). For pindolol it is interesting to note that 16 months oral treatment with 34 mg pindolol a day did not change CO neither at rest nor during exercise in the hypertensive patients. Although HR was significantly reduced in both situations (1).

Thus we find it justified to conclude that the degree of i.s.a. possessed by a given beta-adrenoceptor blocking agent is responsible for the acute changes of HR and CO whereas selectivity is of minor if any importance in this respect.

PATHOPHYSIOLOGICAL MECHANISMS OF THE ANTIHYPERTENSIVE EFFECT OF  
A CARDIOSELECTIVE BETA-ADRENOCEPTOR BLOCKING DRUG (METOPROLOL)

Susanne Ljungman Marianne Hartford Mattias Aurell and  
Göran Berglund

From the Medical Clinic I Sahlgren's Hospital Gothenburg Sweden

Many attempts have been made to identify those hypertensives who could obtain good blood pressure control on beta-adrenoceptor blocking therapy. Reduction of blood pressure has been correlated to the initial sympathetic activity and to different cardiovascular and renal physiological variables in several studies. Hansson (1973) studied 15 selected men of different ages with essential hypertension. He found no correlation between blood pressure reduction on propranolol and variables such as heart rate, cardiac output, peripheral resistance, urinary excretion of catecholamines or plasma renin activity (PRA). Nor did Birkenhäger (1971) or Amery (1976) find that initial PRA or any cardiovascular parameter were suitable predictors of a good blood pressure reduction with propranolol or atenolol.

However, other workers have found initial PRA to be significantly correlated to the blood pressure reduction. Bühler et al (1973) studied the effect of beta adrenoceptor blocking therapy on 74 selected men and women with essential hypertension. Hypertensives with high or normal PRA in relation to their sodium excretion had a good blood pressure reduction, but individuals with low PRA responded poorly. These findings were confirmed by Hollifield et al (1976), Karlberg et al (1976) and by von Bahr et al (1976).

Thus there is uncertainty as to whether factors suitable for guidance to the choice of antihypertensive treatment with beta-adrenoceptor blocking agents exist. The aim of our study was to further analyse the relationship between the antihypertensive effect of the cardioselective beta adrenoceptor blocker metoprolol and factors which are considered to be of importance for maintenance of high

## References.

- 1 Atterhog J -H, Dunér H, and Pernow B Hemodynamic effect of long-term treatment with pindolol in essential hypertension with special reference to the resistance and capacitance vessels of the forearm: *Acta Med. Scand.* 202: 517 1977
- 2 Barrett A.M. The pharmacology of atenolol *Postgraduate Med J* 53, suppl 3 58 1977
- 3 Hansson L. Beta-adrenergic blockade in essential hypertension *Acta Med Scand.* suppl 550 1973
- 4 Jensen, H.Æ . Rasmussen, K and Mosbak N. Clinical and haemodynamic study of atenolol (Tenormin) in essential hypertension, *Clin. Sci Mol Med* 51 525s 1976
- 5 Lund-Johansen P. Haemodynamic long-term effects of atenolol at rest and during exercise in essential hypertension, *Postgraduate Med. J* 53, suppl 3 99 1977
- 6 Tarazi R.C and Dustan H.P Beta-adrenergic blockade in hypertension. Practical and theoretical implications of long-term hemodynamic variation, *Amer J Cardiol* 29 633 1972
- 7 Trap-Jensen J Clausen, J P Noer I Larsen, O A. Krosgaard, A.R. and Christensen, N.J The effects of beta-adrenoceptor blockers on cardiac output, liver blood flow and skeletal muscle blood flow in hypertensive patients *Acta physiol scand.* 98, suppl 440 30 1976

PATHOPHYSIOLOGICAL MECHANISMS OF THE ANTIHYPERTENSIVE EFFECT OF  
A CARDIOSELECTIVE BETA ADRENOCEPTOR BLOCKING DRUG (METOPROLOL)

Susanne Ljungman Marianne Hartford Mattias Aurell and  
Göran Berglund

From the Medical Clinic I Sahlgren's Hospital Gothenburg Sweden

Many attempts have been made to identify those hypertensives who could obtain good blood pressure control on beta-adrenoceptor blocking therapy. Reduction of blood pressure has been correlated to the initial sympathetic activity and to different cardiovascular and renal physiological variables in several studies. Hansson (1973) studied 15 selected men of different ages with essential hypertension. He found no correlation between blood pressure reduction on propranolol and variables such as heart rate, cardiac output, peripheral resistance, urinary excretion of catecholamines or plasma renin activity (PRA). Nor did Birkenhäger (1971) or Amery (1976) find that initial PRA or any cardiovascular parameter were suitable predictors of a good blood pressure reduction with propranolol or atenolol.

However, other workers have found initial PRA to be significantly correlated to the blood pressure reduction. Bühler et al (1973) studied the effect of beta-adrenoceptor blocking therapy on 74 selected men and women with essential hypertension. Hypertensives with high or normal PRA in relation to their sodium excretion had good blood pressure reduction, but individuals with low PRA responded poorly. These findings were confirmed by Hollifield et al (1976), Karlberg et al (1976) and by von Sahr et al (1976).

Thus there is uncertainty as to whether factors suitable for guidance to the choice of antihypertensive treatment with beta adrenoceptor blocking agents exist. The aim of our study was to further analyse the relationship between the antihypertensive effect of the cardioselective beta adrenoceptor blocker metoprolol and factors which are considered to be of importance for maintenance of high

blood pressure. These relations were studied in an unselected epidemiologically defined hypertension population.

### Material

By blood pressure screening of a random sample of 49-year-old men ( $n = 3\ 205$ ) in Gothenburg (participation rate 74%) 74 untreated men with diastolic blood pressure (DBP) over 115 mm Hg were found. 6 persons refused further cooperation but 68 men had their blood pressure measured at least three times at the hypertension out-patient clinic while participating in a routine clinical work-up. The mean of three DBP was  $\geq 100$  mm Hg in 38 of the 68 men. The remaining 30 men had either diastolic blood pressure below 100 mm Hg or had secondary hypertension. Of the 38 men with essential hypertension 9 persons were excluded before treatment was started or during the treatment with metoprolol. Thus totally 29 patients were treated with metoprolol as the only drug for two months. 10 patients belonged to WHO-group I, 18 to WHO-group II and one to WHO-group III.

### Methods

At screening the blood pressure was measured in the seated position without previous rest. At the hypertension clinic the blood pressure was measured in the supine position after five minutes rest. Prior to treatment the patients were subjected to an investigation of cardiac and renal function. Cardiac output was determined by impedance cardiography (Kubicek et al 1970; Granerus et al to be publ). Plasma volume ( $^{131}\text{I}$ -RIHSA), heart volume (calculated from x-ray  $\text{ml/m}^2$  BSA), total peripheral resistance in the leg (calculated from plethysmography and BP) were measured. Left ventricular hypertrophy was estimated by orthogonal ECG according to Frank (the height of the R-wave in lead X) and left ventricular distensibility was expressed as the a/H-ratio on the apex cardiogram. Sodium excretion (mean of three 24-hour-collections) was determined with the patients on free diet. Renal blood flow (PAH-clearance and haematocrite) and renovascular resistance (calculated from renal blood flow and BP) were measured. The PRA and p-aldoosterone (venous plasma samples after 2 hours supine rest at 9-10 a.m.) were analysed according to Giese et al (1970) and radioimmunoassay respectively. P-noradrenaline was determined by an isotope derivative method (Eriksson et al 1977).

The dose of metoprolol was initially 100 mg b i d and was increased after two weeks to 200 mg b i d if the DBP was above 95 mm Hg. The blood pressure was recorded after two, four and eight weeks. Mean blood pressure (MAP) before treatment (the initial pressure) and after two months' treatment were compared. MAP was calculated as  $1/3$  of the pulse pressure + DBP. The reduction of the initial pressure after treatment is expressed in per cent of the initial pressure. Routine statistical methods were used.

## Results

### Reduction of blood pressure

After two months of metoprolol treatment the blood pressure decreased from 163/106 mm Hg to 142/92 mm Hg. The reduction of MAP was 13%. 20 patients had a well controlled blood pressure ( $DBP \leq 95$  mm Hg) on 100 mg b i d and so had 4 patients of the 9 who took 200 mg b i d. Thus 24 of 29 patients (83%) had an adequate blood pressure control with metoprolol only. There was a significant positive correlation between MAP before and MAP after treatment, i.e. the higher the blood pressure was before treatment the higher it was after. No significant correlation was found between the initial blood pressure and the blood pressure reduction either the latter was expressed in absolute figures or in per cent of initial value.

### Cardiac and renal function

There was no correlation between the cardiac index before treatment and the blood pressure reduction ( $r = -0.06$ ). The hypertensives with a high cardiac output thus did not get a better blood pressure reduction than the others. Left ventricular hypertrophy and left ventricular distensibility were not correlated to the blood pressure reduction ( $r = 0.01$  resp.  $0.23$ ). There was no significant correlation between the relative size of the heart according to x-ray and the blood pressure reduction ( $r = 0.28$ ).

The peripheral resistance before treatment was not correlated to the blood pressure reduction ( $r = 0.08$ ) nor was the resistance in the calf muscles after ischemic work ( $r = 0.23$ ). There was no correlation between the BP-reduction and initial renal blood flow ( $r = 0.11$ ), renovascular resistance ( $r = 0.36$ ), u-sodium ( $r = 0.13$ ) or plasma volume ( $r = 0.24$ ).

blood pressure These relations were studied in an unselected epidemiologically defined hypertension population

### Material

By blood pressure screening of a random sample of 49-year-old men ( $n = 3\ 205$ ) in Gothenburg (participation rate 74%) 74 untreated men with diastolic blood pressure (DBP) over 115 mm Hg were found. 8 persons refused further cooperation but 66 men had their blood pressure measured at least three times at the hypertension outpatient clinic while participating in a routine clinical work-up. The mean of three DBP was  $\geq 100$  mm Hg in 38 of the 66 men. The remaining 30 men had either diastolic blood pressure below 100 mm Hg or had secondary hypertension. Of the 38 men with essential hypertension 9 persons were excluded before treatment was started or during the treatment with metoprolol. Thus totally 29 patients were treated with metoprolol as the only drug for two months. 10 patients belonged to WHO-group I, 18 to WHO-group II and one to WHO-group III.

### Methods

At screening the blood pressure was measured in the seated position without previous rest. At the hypertension clinic the blood pressure was measured in the supine position after five minutes rest. Prior to treatment the patients were subjected to an investigation of cardiac and renal function. Cardiac output was determined by impedance cardiography (Kubicek et al 1970; Granerus et al to be publ.). Plasma volume ( $^{131}\text{I}$ -RIHSA), heart volume (calculated from x-ray ml/m<sup>2</sup> BSA), total peripheral resistance in the leg (calculated from plethysmography and BP) were measured. Left ventricular hypertrophy was estimated by orthogonal ECG according to Frank (the height of the R-wave in lead X) and left ventricular distensibility was expressed as the a/H-ratio on the apex cardiogram. Sodium excretion (mean of three 24-hour-collections) was determined with the patients on free diet. Renal blood flow (PAH-clearance and haematocrite) and renovascular resistance (calculated from renal blood flow and BP) were measured. The PRA and p-aldoosterone (venous plasma samples after 2 hours supine rest at 9-10 a.m.) were analysed according to Giese et al (1970) and radioimmunoassay respectively. P-noradrenaline was determined by an isotope derivative method (Eriksson et al 1977).

The dose of metoprolol was initially 100 mg b i d and was increased after two weeks to 200 mg b i d if the DBP was above 95 mm Hg. The blood pressure was recorded after two, four and eight weeks. Mean blood pressure (MAP) before treatment (the initial pressure) and after two months treatment were compared. MAP was calculated as  $1/3$  of the pulse pressure + DBP. The reduction of the initial pressure after treatment is expressed in per cent of the initial pressure. Routine statistical methods were used.

## Results

### Reduction of blood pressure

After two months of metoprolol treatment the blood pressure decreased from 163/106 mm Hg to 142/92 mm Hg. The reduction of MAP was 13%. 20 patients had a well controlled blood pressure ( $DBP \leq 95$  mm Hg) on 100 mg b i d and so had 4 patients of the 9 who took 200 mg b i d. Thus 24 of 29 patients (83%) had an adequate blood pressure control with metoprolol only. There was a significant positive correlation between MAP before and MAP after treatment i.e. the higher the blood pressure was before treatment the higher it was after. No significant correlation was found between the initial blood pressure and the blood pressure reduction either the latter was expressed in absolute figures or in per cent of initial value.

### Cardiac and renal function

There was no correlation between the cardiac index before treatment and the blood pressure reduction ( $r = -0.06$ ). The hypertensives with a high cardiac output thus did not get a better blood pressure reduction than the others. Left ventricular hypertrophy and left ventricular distensibility were not correlated to the blood pressure reduction ( $r = 0.01$  resp.  $0.23$ ). There was no significant correlation between the relative size of the heart according to x ray and the blood pressure reduction ( $r = 0.28$ ). The peripheral resistance before treatment was not correlated to the blood pressure reduction ( $r = 0.08$ ) nor was the resistance in the calf muscles after ischemic work ( $r = 0.23$ ). There was no correlation between the BP-reduction and initial renal blood flow ( $r = 0.11$ ), renovascular resistance ( $r = 0.36$ ), u sodium ( $r = 0.13$ ) or plasma volume ( $r = 0.24$ ).



blood pressure These relations were studied in an unselected epidemiologically defined hypertension population

### Material

By blood pressure screening of a random sample of 49-year-old men ( $n = 3\ 205$ ) in Gothenburg (participation rate 74%) 74 untreated men with diastolic blood pressure (DBP) over 115 mm Hg were found 6 persons refused further cooperation but 68 men had their blood pressure measured at least three times at the hypertension out-patient clinic while participating in a routine clinical work-up The mean of three DBP was  $\geq 100$  mm Hg in 38 of the 68 men The remaining 30 men had either diastolic blood pressure below 100 mm Hg or had secondary hypertension Of the 38 men with essential hypertension 9 persons were excluded before treatment was started or during the treatment with metoprolol Thus totally 29 patients were treated with metoprolol as the only drug for two months 10 patients belonged to WHO-group I 18 to WHO-group II and one to WHO-group III

### Methods

At screening the blood pressure was measured in the seated position without previous rest At the hypertension clinic the blood pressure was measured in the supine position after five minutes rest Prior to treatment the patients were subjected to an investigation of cardiac and renal function Cardiac output was determined by impedance cardiography (Kubicek et al 1970; Granerus et al to be publ ) Plasma volume ( $^{131}\text{I}$ -RIHSA) heart volume (calculated from x-ray  $\text{ml/m}^2$  BSA) total peripheral resistance in the leg (calculated from plethysmography and BP) were measured Left ventricular hypertrophy was estimated by orthogonal ECG according to Frank (the height of the R-wave in lead X) and left ventricular distensibility was expressed as the a/H-ratio on the apex cardiogram Sodium excretion (mean of three 24-hour-collections) was determined with the patients on free diet Renal blood flow (PAH-clearance and haematocrite) and renovascular resistance (calculated from renal blood flow and BP) were measured The PRA and p-aldoosterone (venous plasma samples after 2 hours supine rest at 9-10 a.m.) were analysed according to Glese et al (1970) and radioimmunoassay respectively P-noradrenaline was determined by an isotope derivative method (Eriksson et al 1977)

The dose of metoprolol was initially 100 mg b i d and was increased after two weeks to 200 mg b i d if the DBP was above 95 mm Hg. The blood pressure was recorded after two, four and eight weeks. Mean blood pressure (MAP) before treatment (the initial pressure) and after two months' treatment were compared. MAP was calculated as  $1/3$  of the pulse pressure + DBP. The reduction of the initial pressure after treatment is expressed in per cent of the initial pressure. Routine statistical methods were used.

## Results

### Reduction of blood pressure

After two months of metoprolol treatment the blood pressure decreased from 163/106 mm Hg to 142/92 mm Hg. The reduction of MAP was 13%. 20 patients had a well controlled blood pressure ( $DBP \leq 95$  mm Hg) on 100 mg b i d and so had 4 patients of the 9 who took 200 mg b i d. Thus 24 of 29 patients (83%) had an adequate blood pressure control with metoprolol only. There was a significant positive correlation between MAP before and MAP after treatment, i.e. the higher the blood pressure was before treatment the higher it was after. No significant correlation was found between the initial blood pressure and the blood pressure reduction either the latter was expressed in absolute figures or in per cent of initial value.

### Cardiac and renal function

There was no correlation between the cardiac index before treatment and the blood pressure reduction ( $r = -0.06$ ). The hypertensives with a high cardiac output thus did not get a better blood pressure reduction than the others. Left ventricular hypertrophy and left ventricular distensibility were not correlated to the blood pressure reduction ( $r = 0.01$  resp.  $0.23$ ). There was no significant correlation between the relative size of the heart according to x-ray and the blood pressure reduction ( $r = 0.28$ ).

The peripheral resistance before treatment was not correlated to the blood pressure reduction ( $r = 0.08$ ) nor was the resistance in the calf muscles after ischaemic work ( $r = 0.23$ ). There was no correlation between the BP-reduction and initial renal blood flow ( $r = 0.11$ ), renovascular resistance ( $r = 0.36$ ), u-sodium ( $r = 0.13$ ) or plasma volume ( $r = 0.24$ ).

### Sympathetic activity

Neither p-noradrenaline at rest ( $r = 0.28$ ) u-noradrenaline during daytime ( $r = 0.21$ ) nor initial heart rate ( $r = 0.05$ ) were correlated to the per cent decrease of MAP. Presuming that p-noradrenaline and u-noradrenaline measure the sympathetic activity we could not find that persons with a high sympathetic drive had a better response to beta-adrenoceptor blockade than those with a low sympathetic drive.

### The renin-aldosterone system

A significant positive correlation was found between the blood pressure reduction and the initial PRA ( $r = 0.69$   $p < 0.001$ ). Those with a high PRA before treatment had a good blood pressure reduction and vice versa. No correlation between p-aldosterone and BP-reduction was found ( $r = 0.02$ ).

### Discussion

These results are the first to be presented from a study of pathophysiological mechanisms in essential hypertension. 49-year-old men participated in a blood pressure screening scheme and a subsample underwent extensive investigations of cardiac and renal function. 74 untreated persons with a diastolic blood pressure  $> 115$  mm Hg were found corresponding to a prevalence of 3.1%. We treated 29 men with metoprolol 200-400 mg daily and observed a significant positive correlation between the per cent reduction of the mean arterial blood pressure and the initial PRA. However, there was no correlation to any cardiac or renal parameter or to the sympathetic activity. In contrast to other similar studies so far published, the present one was carried out in hypertensive men homogenous with respect to age and sex. Whether the observed statistical correlation between PRA and the antihypertensive effect reflects a causal relation is not known. This observation supports the hypothesis that the PRA can be used to predict the antihypertensive effect of beta-adrenoceptor blockade. The reason why this relation has been demonstrated in some studies but not in others may well be due to differences in age, sex, race and earlier antihypertensive treatment of the patients studied.

# REFERENCES

- 1 Anery A Billiet L Boel A Fagard R Raybrouck T & Willens J: Mechanism of hypotensive effect during beta-adrenergic blockade in hypertensive patients. Hemodynamic and renin response to a new cardioselective agent; Tanormin or ICI 66 082. *Am Heart J* 91: 634-642 1976
- 2 von Bahr C Collste P Friisk-Holmberg M Haglund K Jorfeldt L Orné M Östman J & Sjöqvist P: Plasma levels and effects of metoprolol on blood pressure, adrenergic beta-receptor blockade and plasma renin activity in essential hypertension. *Clin Pharm Ther* 20: 130-137 1976
- 3 Birkenhager W H Krauss X M Schalekamp M A D B Holsters G & Kroon B U M: Antihypertensive effects of propranolol. Observations on predictability. *Folia Med Neerl* 14: 67-71 1971
- 4 Bühle P R Laragh J M Vaughan E M Jr Brunner H R Gavras H & Baer L: Antihypertensive action of propranolol. *Am J Cardiol* 32: 511-522 1973
- 5 Eriksson B M Andersson I Borg K O & Persson B A: Determination of adrenaline and noradrenaline in plasma by an isotope dilution method and ion pair liquid chromatography. *Acta Pharm Suec* 14: 451-458 1977
- 6 Giese J Jørgensen M Nielsen M D Lund J O & Munck B: Plasma renin concentration measured by use of radioimmunoassay for angiotensin I. *Scand J Clin Lab Invest* 26: 355-367 1970
- 7 Graessig G & Elg R: Stroke volume measurement by impedance cardiography in hypertensive patients. To be published
- 8 Hansson L: Beta-adrenergic blockade in essential hypertension. *Acta Med Scand suppl* 550: 1-40 1973
- 9 Hollifield J W Sherman K Vander Zwagg R & Shand D: Proposed mechanisms of propranolol's antihypertensive effect in essential hypertension. *N Engl J Med* 295: 68-73 1976
- 10 Kallberg B E Kågedal B Tegler L Tolagen M & Bergman B: Controlled treatment of primary hypertension with propranolol and spironolactone. *Amer J Cardiol* 37: 642-649 1976
- 11 Kibicki W G From A H L Patterson R P Witsoe M A Castaneda A Lillehei R C & Ersek R: Journal of the Association for the Advancement of Medical Instrumentation. 1976

# EFFECTS OF METOPROLOL ON ADRENERGIC MECHANISMS DURING LONG- AND SHORT TERM ANTIHYPERTENSIVE TREATMENT OF SPONTANEOUSLY HYPERTENSIVE RATS

B LJUNG B ÅBLAD O ALMGREN C-G DAHLÖF and B-M ERIKSSON

From the Department of Pharmacology AB Hässle Fack S-431 20 Mölndal and Department of Physiology and Pharmacology University of Göteborg Sweden

The antihypertensive effect of  $\beta$ -adrenoceptor antagonists manifests itself in the course of prolonged treatment as a gradual decrease in peripheral resistance. In man cardiac output is similarly reduced by acute and prolonged administration whereas mean arterial pressure (BP) is lowered only by long-term treatment as the reflexly increased peripheral resistance is gradually reduced (Tarazi and Dustan 1972). The mechanism underlying the apparent vasodilatation remains to be clarified. Among the various mechanisms suggested we have studied the possible interference with the adrenergic vasomotor control in experimental animals.

In the spontaneously hypertensive rat (SHR) a single i.v. dose of metoprolol reduced heart rate without affecting BP whereas repeated administration by the i.v. or oral route resulted in BP reduction within the first week of administration (Ljung *et al.* 1976). Furthermore long-term administration of propranolol or metoprolol to growing SHR has been shown to prevent the development of hypertension (Weiss *et al.* 1974). Long-term antihypertensive treatment was found to be associated with impaired vasoconstrictor responses to sympathetic nerve stimulation in the isolated portal vein (Ljung *et al.* 1975) and with reduced rate of adrenal catecholamine synthesis (Åblad *et al.* 1977).

The present experiments were designed to elucidate whether any changes in the adrenergic system found after long-term preventive treatment with the  $\beta_1$ -selective antagonist metoprolol could also be observed after short term curative antihypertensive treatment of adult SHR and thus make it possible to distinguish between secondary changes and primary effects.

## MATERIAL AND METHODS

Female SHR of the Okamoto strain (Møllegaards avlslab A/S) were used. A long-term treated group was fed pelleted food containing 3 mg/g from the age of 6 weeks for 6-5 months. The short-term treated group received control food during the initial 6 months of the study and then the same diet with metoprolol added for two weeks whereas a control group received the standard diet throughout. In the course of the study long-term treated and control rats were housed in metabolic cages for two weeks and urine was collected in acid over 24 h periods during the 2nd week for determination of catecholamines by a radioenzymatic method.

Towards the end of the study chronic catheters were implanted into the aorta via the left femoral artery and exteriorized in the neck in every second rat of each group. At this time metoprolol administration was discontinued. Mean arterial blood pressure and heart rate (HR) were continuously monitored in a computer system during three 2 h sessions during the 2nd and 3rd day after surgery. Values from an individual rat were averaged to give one.

respectively. The animals were then sacrificed and isolated portal vein preparations were mounted in organ baths for studies of vascular neuro-effector function (see Ljung et al 1975). Furthermore hearts are isolated for determination of left ventricular wet weight and adrenals were frozen after rapid dissection for determination of dopamine (DA) content.

Locomotor activity was recorded in rats not subjected to BP measurement. The animals were placed in exptl cages and spontaneous movements were recorded during the initial 10 min period by a photo-electric method.

In a separate set of experiments adult female SHR were treated with metoprolol 3 mg/g for 8 weeks. The animals were then decapitated and their hearts, portal veins, superior mesenteric arteries and adrenals were rapidly isolated for determination of endogenous NA content by means of a radioenzymatic method.

## RESULTS

The results are summarized in table I.

Table I

Effects of oral metoprolol (3 mg/g food) treatment of SHR for 6.5 months during development of hypertension (long-term treatment) or during two weeks at adult age (short-term treatment). Mean  $\pm$  SE.

Variable	Control C	Long-term treatment L	Short-term treatment S
Mean arterial blood pressure (mmHg)	181 $\pm$ 5    n=6	149 $\pm$ 4    n=7	157 $\pm$ 5    n=9
Heart rate (bpm)	387 $\pm$ 8	376 $\pm$ 10	394 $\pm$ 8
Body weight (g)	251 $\pm$ 5	226 $\pm$ 5	235 $\pm$ 6
Left ventricular weight (% of BW)	0.33 $\pm$ 0.01	0.29 $\pm$ 0.01 $\Delta$	0.35 $\pm$ 0.01
Adrenal DA content (nmoles)	2.68 $\pm$ 0.52	1.35 $\pm$ 0.09	1.78 $\pm$ 0.18
Urinary NA (nmol/d)	8.57 $\pm$ 0.37    n=9	9.52 $\pm$ 0.43    n=9	
Urinary DA (nmol/d)	31.5 $\pm$ 1.37	33.0 $\pm$ 0.90	
Locomotor activity (counts)	179 $\pm$ 13.3    n=10	187 $\pm$ 11.4    n=11	168 $\pm$ 13.8    n=8
Portal vein NA -log ED <sub>50</sub> (M)	6.11 $\pm$ 0.06    n=7	6.11 $\pm$ 0.06    n=7	6.06 $\pm$ 0.07    n=8
Portal vein NA -log f <sub>50</sub> (Hz)	0.60 $\pm$ 0.02	0.58 $\pm$ 0.02 $\Delta$	0.64 $\pm$ 0.02

Indicates  $p < 0.05$  as compared to control.

$\Delta$  Indicates  $p < 0.05$  as compared to short-term treatment.

The mean arterial blood pressure was significantly lowered in both of the treated groups as compared to control whereas no significant difference was found between the pressure levels after long-term and short-term treatment respectively. Heart rate was the same in all three groups indicating that no significant  $\beta$ -adrenoceptor blocked prevailed at the time of recording. The left ventricular weight expressed as a percentage of body weight was lowered after long-term preventive treatment and after 8 weeks curative treatment but not after short-term treatment.

# EFFECTS OF METOPROLOL ON ADRENERGIC MECHANISMS DURING LONG- AND SHORT-TERM ANTIHYPERTENSIVE TREATMENT OF SPONTANEOUSLY HYPERTENSIVE RATS

B LJUNG B RBLAD O ALMGREN C-G DAHLÖF and B-M ERIKSSON

From the Department of Pharmacology AB Hässle Fack S-431 20 Mölndal and Departments of Physiology and Pharmacology University of Göteborg Sweden

The antihypertensive effect of  $\beta$ -adrenoceptor antagonists manifests itself in the course of prolonged treatment as a gradual decrease in peripheral resistance. In man cardiac output is similarly reduced by acute and prolonged administration whereas mean arterial pressure (BP) is lowered only by long-term treatment as the reflexly increased peripheral resistance is gradually reduced (Tarazi and Dustan 1972). The mechanism underlying the apparent vasodilatation remains to be clarified. Among the various mechanisms suggested we have studied the possible interference with the adrenergic vasomotor control in experimental animals.

In the spontaneously hypertensive rat (SHR) a single i.v. dose of metoprolol reduced heart rate without affecting BP whereas repeated administration by the i.v. or oral route resulted in BP reduction within the first week of administration (Ljung *et al.* 1976). Furthermore long-term administration of propranolol or metoprolol to growing SHR has been shown to prevent the development of hypertension (Weiss *et al.* 1974). Long-term antihypertensive treatment was found to be associated with impaired vasoconstrictor responses to sympathetic nerve stimulation in the isolated portal vein (Ljung *et al.* 1975) and with reduced rate of adrenal catecholamine synthesis (Rblad *et al.* 1977).

The present experiments were designed to elucidate whether any changes in the adrenergic system found after long-term preventive treatment with the  $\beta_1$ -selective antagonist metoprolol could also be observed after short term curative antihypertensive treatment of adult SHR and thus make it possible to distinguish between secondary changes and primary effects.

## MATERIAL AND METHODS

Female SHR of the Okamoto strain (Møllegaards avlslab A/S) were used. A long-term treated group was fed pelleted food containing 3 mg/g from the age of 6 weeks for 6.5 months. The short-term treated group received control food during the initial 6 months of the study and then the same diet with metoprolol added for two weeks whereas a control group received the standard diet throughout. In the course of the study long-term treated and control rats were housed in metabolic cages for two weeks and urine was collected in acid over 24 h periods during the 2nd week for determination of catecholamines by a radioenzymatic method.

Towards the end of the study chronic catheters were implanted into the aorta via the left femoral artery and exteriorized in the neck in every second rat of each group. At this time metoprolol administration was discontinued. Mean arterial blood pressure and heart rate (HR) were continuously monitored in a computer based system during three 2 h sessions during the 2nd and 3rd day after surgery. All values from an individual rat were averaged to give one reading of BP and HR.

respectively. The animals were then sacrificed and isolated portal vein preparations were mounted in organ baths for studies of vascular neuro-effector function (see Ljung et al 1975). Furthermore hearts were isolated for determination of left ventricular wet weight and adrenals were frozen after rapid dissection for determination of dopamine (DA) content.

Locomotor activity was recorded in rats not subjected to BP measurement. The animals were placed in exptl cages and spontaneous movements were recorded during the initial 10 min period by a photo-electric method.

In a separate set of experiments adult female SHR were treated with metoprolol 3 mg/g for 8 weeks. The animals were then decapitated and their hearts, portal veins, superior mesenteric arteries and adrenals were rapidly isolated for determination of endogenous NA content by means of a radioenzymatic method.

## RESULTS

The results are summarized in table I.

Table I

Effects of oral metoprolol (3 mg/g food) treatment of SHR for 6.5 months during development of hypertension (long-term treatment) or during two weeks at adult age (short-term treatment). Mean  $\pm$  SE.

Variable	Control C	Long-term treatment L	Short-term treatment S
Mean arterial blood pressure (mmHg)	181 $\pm$ 5    n=6	149 $\pm$ 4    n=7	157 $\pm$ 5    n=9
Heart rate (bpm)	387 $\pm$ 8	376 $\pm$ 10	394 $\pm$ 8
Body weight (g)	251 $\pm$ 5	226 $\pm$ 5	235 $\pm$ 6
Left ventricular weight (% of BW)	0.33 $\pm$ 0.01	0.29 $\pm$ 0.01 <sup>A</sup>	0.35 $\pm$ 0.01
Adrenal DA content (nmoles)	2.68 $\pm$ 0.52	1.55 $\pm$ 0.09	1.78 $\pm$ 0.18
Urinary NA (nmol/d)	8.57 $\pm$ 0.37    n=9	9.52 $\pm$ 0.43    n=9	
Urinary DA (nmol/d)	31.5 $\pm$ 1.37	33.0 $\pm$ 0.90	
Locomotor activity (counts)	179 $\pm$ 13.3    n=10	187 $\pm$ 11.4    n=11	168 $\pm$ 13.8    n=8
Portal vein NA log ED <sub>50</sub> (M)	6.11 $\pm$ 0.06    n=7	6.11 $\pm$ 0.06    n=7	6.06 $\pm$ 0.07    n=8
Portal vein NS -log f <sub>50</sub> (Hz)	0.60 $\pm$ 0.02	0.58 $\pm$ 0.02 <sup>A</sup>	0.64 $\pm$ 0.02

<sup>A</sup> indicates p < 0.05 as compared to control.

<sup>A</sup> indicates p < 0.05 as compared to short-term treatment.

The mean arterial blood pressure was significantly lowered in both of the treated groups as compared to control whereas no significant difference was found between the pressure levels after long-term and short-term treatment, respectively. Heart rate was the same in all three groups indicating that no significant  $\beta$ -adrenoceptor blockade prevailed at the time of recording. The left ventricular weight expressed as a percentage of body weight was lowered after long-term, preventive treatment and after 8 weeks curative treatment but not after short-term treatment.



In the isolated portal vein preparation there was no apparent difference in the spontaneous myogenic activity nor in the maximum force generated in response to NA. The sensitivity to exogenous NA ( $\log ED_{50}$  value) was not different in the three groups and the responses to transmural nerve stimulation were likewise comparable. After  $\alpha$ -adrenoceptor blockade isoprenaline readily caused inhibition of the myogenic activity in portal veins from all three groups.

The adrenals were analyzed for dopamine (DA) content as an index of sympatho-adrenal discharge (see discussion). The DA levels were markedly reduced in the adrenals of SHR exposed to long-term as well as short-term treatment as compared to control. On the other hand the daily urinary output of NA or DA was not different in SHR exposed to long-term treatment. For technical reasons catecholamine excretion was not tested in rats subjected to short-term metoprolol treatment. Exploratory behavior measured as locomotor activity during an initial 10 min period was not interfered with by metoprolol treatment.

In SHR treated with metoprolol for 8 weeks the relative cardiac weight was significantly lower ( $0.39 \pm 0.006$  %  $n=7$ ) than in control SHR ( $0.42 \pm 0.015$  %  $n=5$ ). The cardiac NA content was slightly elevated ( $5.2 \pm 0.30$  vs  $4.4 \pm 0.24$  nmoles) like in the adrenals ( $109 \pm 3.7$  vs  $87 \pm 2.9$  nmoles) and in the portal vein ( $11.4 \pm 1.07$  vs  $8.9 \pm 0.65$  nmoles/g) in the treated rats compared to control. Although not statistically significant the same tendency of increased NA level was found in the superior mesenteric artery ( $8.6 \pm 0.89$  vs  $7.7 \pm 0.89$  nmoles/g).

#### DISCUSSION

In accordance with earlier studies long-term treatment of SHR with metoprolol during development of hypertension (Weiss et al 1974, Ljung et al 1975) and short-term treatment during established hypertension (Ljung et al 1976) resulted in lowered blood pressure as compared to control. As previously discussed (Ljung et al 1976) the antihypertensive effect of metoprolol in SHR resembles that in hypertensive patients with regard to time of onset, extent of response and plasma concentrations of metoprolol required.

In contrast to previous findings (Ljung et al 1975) however the neurogenic responses of the isolated portal vein were not depressed after long-term treatment. This does not necessarily imply a qualitative difference between the effects of metoprolol on the peripheral neuro-effector function in the two studies. Acute blockade of the prejunctional  $\beta$ -adrenoceptor mediated positive feed-back mechanism in isolated portal vein of SHR by dl-propranolol causes a reduction in transmitter release per impulse of up to 30 per cent without depression of the effector response (Dahlöf et al 1978). Thus reduced transmitter output may have occurred during nerve stimulation in the tissues from the treated animals but

the extent of reduction has not been sufficiently large to attenuate responses

The findings of a lowered DA content in the adrenals both after short and long-term metoprolol treatment indicate a reduced rate of catecholamine synthesis which may reflect reduced rate of discharge in the adrenergic system (Carlsson et al 1973). In subsequent experiments (Ålmgren unpublished) it has been shown that the depression of the rate of adrenal catecholamine synthesis during metoprolol treatment is indeed mediated via nervous mechanisms rather than a direct effect of the agent on the adrenal medulla. The slight increase in NA content of the heart, the blood vessels and in the adrenals found after 8 weeks metoprolol treatment may support this tenet (cf Carlsson et al 1977). In the rabbit Raine and Chubb (1977) have found biochemical support for and Lewis and Haessler (1975) electrophysiological evidence of reduced rate of sympathetic nerve discharge during prolonged administration of  $\beta$ -adrenoceptor antagonists. It is of interest that the urinary excretion of NA was not lowered in long-term treated SHR. Thus the amount of intact NA recovered in the urine may not adequately reflect the sympathetic activity of the animal. The rats were not sedated by the metoprolol treatment as apparent from the lack of effect on exploratory behavior. This refutes the possibility that BP and sympathetic activity were simply reduced secondary to an overall decrease in mental or physical activity.

In conclusion the present experiments demonstrate that metoprolol during long-term preventive treatment and during short-term curative treatment causes reduced BP in the SHR. The results point to a primary involvement of the adrenergic cardiovascular control mechanisms and we conclude that a reduced rate of discharge is one mechanism by which metoprolol exerts its antihypertensive effect in SHR.

#### REFERENCES

- ÅBLAD B, O. ÅLMGREN, A. CARLSSON, M. HENNING, J. JONASSEN and B. LJUNG. Reduced adrenal amine synthesis in spontaneously hypertensive rats after long-term treatment with propranolol. Br. J. Pharmacol. 1977 61:318-320.
- CARLSSON A, S. R. SNIDER, O. ÅLMGREN and M. LINDQVIST. The neurogenic short-term control of catecholamine synthesis and release in the sympatho-adrenal system as effected in the levels of endogenous dopamine and  $\beta$ -hydroxylated catecholamines. I: Frontiers in Catecholamine Research. Eds E. Usdin and S. Snyder. Pergamon Press, New York 1973. pp 551-556.
- DAHLB F, B. LJUNG and B. ÅBLAD. Presynaptic  $\beta$ -adrenoceptor mediated facilitation of noradrenaline release in rat portal vein (Abstr.) Acta physiol scand 1978 102: 65A.
- LEWIS P. J. and G. HAEUSSLER. Reduction of sympathetic nervous activity as a mechanism of the hypotensive effect of propranolol. Nature (Lond) 1975 256: p 440.
- LJUNG B, B. ÅBLAD, F. DAHLB, M. HENNING and E. MULLBERG. Impaired vasoconstrictor nerve function in spontaneously hypertensive rats after long-term treatment with propranolol and metoprolol. Blood Vessels 1975 12:311-315.

In the isolated portal vein preparation there was no apparent difference in the spontaneous myogenic activity nor in the maximum force generated in response to MA. The sensitivity to exogenous MA ( $\log ED_{50}$  value) was not different in the three groups and the responses to transmural nerve stimulation were likewise comparable. After  $\alpha$ -adrenoceptor blockade isoprenaline readily caused inhibition of the myogenic activity in portal veins from all three groups.

The adrenals were analyzed for dopamine (DA) content as an index of sympatho-adrenal discharge (see discussion). The DA levels were markedly reduced in the adrenals of SHR exposed to long-term as well as short-term treatment as compared to control. On the other hand the daily urinary output of MA or DA was not different in SHR exposed to long-term treatment. For technical reasons catecholamine excretion was not tested in rats subjected to short-term metoprolol treatment. Exploratory behavior measured as locomotor activity during an initial 10 min period was not interfered with by metoprolol treatment.

In SHR treated with metoprolol for 8 weeks the relative cardiac weight was significantly lower ( $0.39 \pm 0.006$  g,  $n=7$ ) than in control SHR ( $0.42 \pm 0.015$  g,  $n=5$ ). The cardiac MA content was slightly elevated ( $5.2 \pm 0.30$  vs  $4.4 \pm 0.24$  nmoles) like in the adrenals ( $109 \pm 3.7$  vs  $87 \pm 2.9$  nmoles) and in the portal vein ( $11.4 \pm 1.07$  vs  $8.9 \pm 0.65$  nmoles/g) in the treated rats compared to control. Although not statistically significant the same tendency of increased MA level was found in the superior mesenteric artery ( $8.6 \pm 0.89$  vs  $7.7 \pm 0.89$  nmoles/g).

#### DISCUSSION

In accordance with earlier studies long-term treatment of SHR with metoprolol during development of hypertension (Weiss et al 1974, Ljung et al 1975) and short-term treatment during established hypertension (Ljung et al 1976) resulted in lowered blood pressure as compared to control. As previously discussed (Ljung et al 1976) the antihypertensive effect of metoprolol in SHR resembles that in hypertensive patients with regard to time of onset, extent of response and plasma concentrations of metoprolol required.

In contrast to previous findings (Ljung et al 1975) however the neurogenic responses of the isolated portal vein were not depressed after long-term treatment. This does not necessarily imply a qualitative difference between the effects of metoprolol on the peripheral neuro-effector function in the two studies. Acute blockade of the prejunctional  $\beta$ -adrenoceptor mediated positive feedback mechanism in isolated portal vein of SHR by dl-propranolol causes a reduction in transmitter release per impulse of up to 30 per cent without depression of the effector response (Dahlöf et al 1978). Thus reduced transmitter output may have occurred during nerve stimulation in the tissues from the treated animals but

the extent of reduction has not been sufficiently large to attenuate responses

The findings of a lowered DA content in the adrenals both after short and long-term metoprolol treatment indicate a reduced rate of catecholamine synthesis which may reflect reduced rate of discharge in the adrenergic system (Carlsson et al 1973). In subsequent experiments (Ålmgren unpublished) it has been shown that the depression of the rate of adrenal catecholamine synthesis during metoprolol treatment is indeed mediated via nervous mechanisms rather than a direct effect of the agent on the adrenal medulla. The slight increase in NA content of the heart, the blood vessels and in the adrenals found after 8 weeks metoprolol treatment may support this tenet (cf Carlsson et al 1977). In the rabbit Raine and Chubb (1977) have found biochemical support for and Lewis and Häusler (1975) electrophysiological evidence of reduced rate of sympathetic nerve discharge during prolonged administration of  $\beta$ -adrenoceptor antagonists. It is of interest that the urinary excretion of NA was not lowered in long-term treated SHR. Thus the amount of intact NA recovered in the urine may not adequately reflect the sympathetic activity of the animal. The rats were not sedated by the metoprolol treatment as apparent from the lack of effect on exploratory behavior. This refutes the possibility that BP and sympathetic activity were simply reduced secondary to an overall decrease in mental or physical activity.

In conclusion the present experiments demonstrate that metoprolol during long-term preventive treatment and during short-term curative treatment causes reduced BP in the SHR. The results point to a primary involvement of the adrenergic cardiovascular control mechanisms and we conclude that a reduced rate of discharge is one mechanism by which metoprolol exerts its antihypertensive effect in SHR.

#### REFERENCES

- ÅBLAD B, O ÅLMGREN A, CARLSSON R, HENNING J, JONASSEN and B LJUNG. Reduced adrenal amine synthesis in spontaneously hypertensive rats after long-term treatment with propranolol. Br. J. Pharmacol. 1977 61:318-320.
- CARLSSON A, S R SNIDER O ÅLMGREN and M LINDQVIST. The neurogenic short-term control of catecholamine synthesis and release in the sympatho-adrenal system as reflected in the levels of endogenous dopamine and 8-hydroxylated catecholamines. In Frontiers in Catecholamine Research. Eds E Uddin and S Snyder. Pergamon Press, New York 1973 pp 551-556.
- DAHLÖF E, B LJUNG and B ÅBLAD. Presynaptic  $\beta$ -adrenoceptor mediated facilitation of noradrenaline release in rat portal vein (Abstract). Acta physiol. scand. 1978 102: 65A.
- LEWIS P J and G HÄUSLER. Reduction of sympathetic nervous activity as a mechanism of the hypotensive effect of propranolol. Nature (Lond) 1975 256 p 440.
- LJUNG B, B ÅBLAD C DAHLÖF M HENNING and E MÖLTERBERG. Impaired vasoconstrictor nerve function in spontaneously hypertensive rats after long-term treatment with propranolol and metoprolol. Blood Vessels 1975 12:311-315.

In the isolated portal vein preparation there was no apparent difference in the spontaneous myogenic activity nor in the maximum force generated in response to NA. The sensitivity to exogenous NA ( $\log ED_{50}$  value) was not different in the three groups and the responses to transneuronal nerve stimulation were likewise comparable. After  $\alpha$ -adrenoceptor blockade isoprenaline readily caused inhibition of the myogenic activity in portal veins from all three groups.

The adrenals were analyzed for dopamine (DA) content as an index of sympatho-adrenal discharge (see discussion). The DA levels were markedly reduced in the adrenals of SHR exposed to long-term as well as short-term treatment as compared to control. On the other hand the daily urinary output of NA or DA was not different in SHR exposed to long-term treatment. For technical reasons catecholamine excretion was not tested in rats subjected to short-term metoprolol treatment. Exploratory behavior measured as locomotor activity during an initial 10 min period was not interfered with by metoprolol treatment.

In SHR treated with metoprolol for 8 weeks the relative cardiac weight was significantly lower ( $0.39 \pm 0.006$  g,  $n=7$ ) than in control SHR ( $0.42 \pm 0.015$  g,  $n=5$ ). The cardiac NA content was slightly elevated ( $5.2 \pm 0.30$  vs  $4.4 \pm 0.24$  nmoles) like in the adrenals ( $109 \pm 3.7$  vs  $87 \pm 2.9$  nmoles) and in the portal vein ( $11.4 \pm 1.07$  vs  $8.9 \pm 0.65$  nmoles/g) in the treated rats compared to control. Although not statistically significant the same tendency of increased NA level was found in the superior mesenteric artery ( $8.6 \pm 0.89$  vs  $7.7 \pm 0.89$  nmoles/g).

#### DISCUSSION

In accordance with earlier studies long-term treatment of SHR with metoprolol during development of hypertension (Weiss et al 1974, Ljung et al 1975) and short-term treatment during established hypertension (Ljung et al 1976) resulted in lowered blood pressure as compared to control. As previously discussed (Ljung et al 1976) the antihypertensive effect of metoprolol in SHR resembles that in hypertensive patients with regard to time of onset, extent of response and plasma concentrations of metoprolol required.

In contrast to previous findings (Ljung et al 1975) however the neurogenic responses of the isolated portal vein were not depressed after long-term treatment. This does not necessarily imply a qualitative difference between the effects of metoprolol on the peripheral neuro-effector function in the two studies. Acute blockade of the prejunctional  $\beta$ -adrenoceptor mediated positive feedback mechanism in isolated portal vein of SHR by dl-propranolol causes a reduction in transmitter release per impulse of up to 30 per cent without depression of the effector response (Dahlöf et al 1978). Thus reduced transmitter output may have occurred during nerve stimulation in the tissues from the treated animals but

## BETA ADRENERGIC BLOCKADE AND VASOSPASM

Olav Thulesius

From the department of Clinical Physiology Regional  
Hospital Trondheim Norway

### INTRODUCTION

Vasospastic disorders of the digital circulation such as Raynaud-phenomena are known side-effects of treatment with beta-adrenergic blockade (Marshall et al 1976). To the present time there is no satisfactory explanation of the underlying patho-physiological mechanism. We therefore studied the digital circulation in 3 patients with beta blocker-induced Raynaud-phenomena.

### METHODS

The method employed is based on measurement of critical closing pressure in the digits using strain-gauges applied to the distal phalanx and a small tourniquet encircling the middle phalanx. The pressure changes in this cuff were induced by water which at the same time also could be used for local cooling of the digit. Changes in finger temperature were elicited by perfusion with water at different temperatures (30-5°C). An additional cuff on the same digit applied to the proximal phalanx was used to arrest the circulation during the cooling procedure. Control pressure was recorded in the arm and another finger. The method has been introduced by Nielsen et al (1978).

### RESULTS

Three patients treated with beta-blockers (propranolol and metoprolol) who developed Raynaud-phenomena were investigated during and 3 weeks after withdrawal of treatment. Fractional digital pressure determined with strain-gauge technique upon cooling is shown in table I. It can be seen that although systemic blood pressure was unchanged pressure drop in the digital arteries was less pronounced in all three cases. In case No. 2 critical closing of the digital circulation occurred at 5°C during treatment with metoprolol but after withdrawal this was eliminated.

- LJUNG B B BJBLAD L DREWS E FELLENIUS A KJELLSTEDT and M WALLBORG  
Antihypertensive effect of metoprolol in spontaneously hypertensive rats  
Clin. Sci Mol Med 1976 51 443s-445s
- RAINE A E G and I W CHUBB Long-term  $\beta$ -adrenergic blockade reduces tyrosine  
hydroxylase and dopamine  $\beta$ -hydroxylase activities in sympathetic ganglia  
Nature (Lond) 1977 267 265-267
- TARAZI R C and H P DUSTAN Beta adrenergic blockade in hypertension Practical  
and theoretical implications of long-term haemodynamic variations Am J  
Cardiol 1972 29 633-640
- WEISS L Y LUNDGREN and B FOLKOW Effects of prolonged treatment with  
adrenergic  $\beta$ -receptor antagonists on blood pressure cardiovascular design  
and reactivity in spontaneously hypertensive rats (SHR) Acta physiol scand  
1974 91 447-457

Supported by the Swedish Medical Research Council 3884 2862

		Temperature in digit Co					BP	Drug
		35	30	20	10	5		
1	before	0 95	1 05	1 02	0 65	0 50	155/95	Propranolol
	after	1 00	1 00	0 90	0 78	0 75	150/95	
2	before	1 00	1 00	0 94	0 45	0	145/80	Metoprolol
	after	0 90	0 90	0 65	0 31	0 24	150/80	
3	before	1 08	1 05	1 02	0 65	0 50	155/95	Propranolol
	after	1 00	1 00	1 09	0 78	0 90	150/95	

Table I Digital arterial blood pressure during gradual local cooling Digital pressure expressed as fraction of control finger pressure blood pressure in brachial artery

#### References

- 1 Hansson, B G Long term non-selective and cardio-selective beta-receptor blockade in hypertensive patients *Acta Med Scand suppl* 598 1976
- 2 Marshall, A J , Roberts, C J C and Barrit, D W : Raynaud's phenomenon as a side effect of beta-blockers in hypertension *Brit Med J* 1 1948 1976
- 3 Niel sen, S L , Lassen, N A Cold sensitivity of digital arteries evaluated by measurement of systolic blood pressure after local cooling *G Appl Physiol* 1978 (in press)
- 4 Simpson, W T : Nature and incidence of unwanted effects with atenolol *Postgrad Med J* 53 Suppl 3 1977



## DISCUSSION

Raynaud-phenomena seem to occur more frequently with beta-blockers as compared to other types of antihypertensive treatment (cf Marshall et al 1976) Beta blockers seem to enhance vascular tone in certain areas and especially cutaneous vessels. This is not apparent clinically except in patients prone to develop Raynaud-phenomena presumably due to an increased vasoconstrictor activity of the digital arteries. This could be shown in the present study since critical closing pressure in the digits was reversibly affected by various beta-blockers. A reasonable explanation may be enhanced neurogenic alpha-adrenergic tone. Moreover an increased humoral stimulation by circulating catecholamines is a possible explanation since it has been shown that both non-selective and cardioselective beta-receptor blockade leads to enhanced noradrenaline responses in connection with stress such as physical exercise (Hansson 1976). Elimination of a tonic beta 2 stimulation does not seem to be a reasonable explanation for the development of this circulatory disturbance since it is caused both by selective and non-selective beta-blockers and the prevalence of cold extremities was equal in patients treated with the cardio-selective beta blocker Atenolol and Propranolol (Simpson 1977).

In 50 cases with intermittent claudication we found equal proportions of patients on beta-blockers and other types of antihypertensive treatment. Contrary to disturbances of the cutaneous circulation such as cold extremities and Raynaud-phenomena intermittent claudication does not seem to be specifically related to beta-blockade but rather any blood pressure lowering treatment as such.

		Temperature in digit Co					BP	Drug
		35	30	20	10	5		
1	before	0 95	1 05	1 02	0 65	0 50	155/95	Propranolol
	after	1 00	1 00	0 90	0 78	0 75	150/95	
2	before	1 00	1 00	0 94	0 45	0	145/80	Metoprolol
	after	0 90	0 90	0 65	0 31	0 24	150/80	
3	before	1 08	1 05	1 02	0 65	0 50	155/95	Propranolol
	after	1 00	1 00	1 09	0 78	0 90	150/95	

Table I Digital arterial blood pressure during gradual local cooling Digital pressure expressed as fraction of control finger pressure blood pressure in brachial artery

#### References

- 1 Hansson, B G : Long term non-selective and cardio-selective beta-receptor blockade in hypertensive patients Acta Med Scand suppl 598 1976
- 2 Marshall, A J , Roberts, C J C and Barrit, D W : Raynaud s phenomenon as a side effect of beta-blockers in hypertension Brit Med J 1:1948 1976
- 3 Nielsen, S L , Lassen, N A Cold sensitivity of digital arteries evaluated by measurement of systolic blood pressure after local cooling Q Appl Physiol 1978 (in press)
- 4 Simpson, W T Nature and incidence of unwanted effects with atenolol Postgrad Med J 53 Suppl 3 1977

## EFFECT OF BETA BLOCKADE ON LEG BLOOD FLOW AND LACTATE RELEASE IN EXERCISING MAN

Hans Aström and Anders Juhlin Dannfelt

From the Department of Clinical Physiology Huddinge Hospital Karolinska Institute S 414 86 Huddinge Sweden

Adrenergic mechanisms are involved in the regulation of both circulation and metabolism in the extremities. Thus beta adreno-receptor blockade with propranolol has been shown to effectively block the vasodilator effect of catecholamines in the forearm at rest (1-7). Less is known about the effect of betablockade on peripheral vessels during exercise but after long term treatment it has been reported both a decrease in leg blood flow (12) and no decrease (3).

Although beta adrenergic mechanisms are involved in both carbohydrate and lipid metabolism treatment with therapeutic doses of betablocking drugs has been reported to induce only slight metabolic changes. Concerning muscle metabolism chronic treatment with alprenolol decreases the lactate release during exercise despite somewhat higher muscle lactate concentrations (3-4). It is not known whether this also applies during acute blockade and could contribute to the muscle fatigue experienced by some patients on betablockers.

### Material and Methods

Nine healthy male volunteers participated in the study. Teflon catheters were inserted percutaneously into the femoral artery and vein of both legs. The tips of the catheters were placed 1-2 cm above the inguinal ligament.

The subjects were studied at rest in the supine position and during 15 min upright continuous bicycle exercise at a work load corresponding to approximately 50 % of their maximal oxygen capacity. After exercise the subjects rested for 45 min whereupon 2 mg propranolol in 10 ml saline was slowly infused during 5 min in the femoral artery of the right leg. Ten minutes later the study was repeated exactly as before the blockade. To test the blockade adrenaline was given intra venously as a constant infusion ( $0.1 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ ) in five subjects and after 10 min the determinations at rest were done. Ten minutes after stopping the adrenaline infusion the subjects performed the second exercise test.

Leg blood flow was determined by constant intra arterial infusion of indocyanine green dye with sampling in the femoral veins (8) Both at rest and during exercise leg blood flow determinations were made in both legs in randomized order

Arterial and femoral venous blood samples were collected simultaneously at timed intervals for oxygen saturation and lactate determinations

Arterial blood pressure was recorded and the resistance over the vascular bed of the leg was calculated as mean femoral artery pressure (mm Hg) divided by leg blood flow (l/min)

## Results

Leg blood flow averaged  $0.50 \pm 0.06$  l/min and there was no difference between the right and left leg (Fig 1a) After betablockade leg blood flow remained unchanged in both legs but when adrenaline was given a 100 % increase appeared in the unblocked leg ( $p < 0.05$ ) Due to the increased flow leg vascular resistance decreased after adrenaline but remained unchanged in the blocked leg The arterial femoral venous oxygen difference did not change significantly in the blocked leg when adrenaline was infused resulting in an unchanged leg oxygen uptake In the unblocked leg however adrenaline gave a small increase in leg oxygen uptake ( $p < 0.05$ )

The arterial lactate concentration averaged  $0.59 \pm 0.11$  mmol/l at rest and increased after adrenaline to  $0.93 \pm 0.13$  mmol/l ( $p < 0.01$ ) The release calculated as the product of leg blood flow and femoral venous arterial difference was  $0.06 \pm 0.01$  mmol/min in the test leg and  $0.07 \pm 0.01$  in the control leg After adrenaline the release was abolished in the betablocked leg ( $p < 0.05$ ) whereas it increased in the control leg ( $p < 0.05$ )(Fig 1b)

Exercise At the two exercise periods heart rate increased to a mean of  $117 \pm 3$  and was the same before and after betablockade Both systolic and diastolic blood pressure were uninfluenced by the local betablockade The blood flow in the blocked leg was also unchanged compared both with before propranolol injection and with the contra lateral leg which thus also reflects an unchanged leg resistance (Fig 1a)

The arterial lactate concentration was lower during the second

## EFFECT OF BETA BLOCKADE ON LEG BLOOD FLOW AND LACTATE RELEASE IN EXERCISING MAN

Hans Aström and Anders Juhlin Dannfelt

From the Department of Clinical Physiology Huddinge Hospital Karolinska Institute S 414 86 Huddinge Sweden

Adrenergic mechanisms are involved in the regulation of both circulation and metabolism in the extremities. Thus beta adrenoceptor blockade with propranolol has been shown to effectively block the vasodilator effect of catecholamines in the forearm at rest (1-7). Less is known about the effect of betablockade on peripheral vessels during exercise but after long term treatment it has been reported both a decrease in leg blood flow (12) and no decrease (3).

Although beta adrenergic mechanisms are involved in both carbohydrate and lipid metabolism treatment with therapeutic doses of betablocking drugs has been reported to induce only slight metabolic changes. Concerning muscle metabolism chronic treatment with alprenolol decreases the lactate release during exercise despite somewhat higher muscle lactate concentrations (3-4). It is not known whether this also applies during acute blockade and could contribute to the muscle fatigue experienced by some patients on betablockers.

### Material and Methods

Nine healthy male volunteers participated in the study. Teflon catheters were inserted percutaneously into the femoral artery and vein of both legs. The tips of the catheters were placed 1-2 cm above the inguinal ligament.

The subjects were studied at rest in the supine position and during 15 min upright continuous bicycle exercise at a work load corresponding to approximately 50 % of their maximal oxygen capacity. After exercise the subjects rested for 45 min whereupon 2 mg propranolol in 10 ml saline was slowly infused during 5 min in the femoral artery of the right leg. Ten minutes later the study was repeated exactly as before the blockade. To test the blockade adrenaline was given intra venously as a constant infusion ( $0.1 \mu\text{g kg}^{-1} \text{ min}^{-1}$ ) in five subjects and after 10 min the determinations at rest were done. Ten minutes after stopping the adrenaline infusion the subjects performed the second exercise test.

## Discussion

The main finding in the present study is the marked decrease in lactate release from the leg after acute beta adrenoreceptor blockade with a reduction by almost 50 % during exercise. No definite explanation for this can be given but it is worth noting that in the cat skeletal muscle a beta adrenergic dilator response can be evoked during sympathetic stimulation (10). The neurogenic  $\beta$ -dilatation is confined to the small resistance vessels with little influence on total flow. Furthermore the latter study shows that the dilator response can be eliminated by propranolol with a reduction of the transcapillary fluid absorption by 50 % and hence a reduction of the available capillary surface. This could explain the decrease in lactate release found in the present study as a result of a mass transport mechanism despite an unchanged total leg blood flow.

Another possible explanation for the reduced lactate release could however be a reduced glycogenolysis with less production of lactate. No measurement of muscle lactate was done in this study but earlier results both after acute propranolol treatment in dogs (11) and chronic treatment with alprenolol (4) have shown an increased glycogenolysis after  $\beta$ -blockade. Furthermore in the latter study higher concentrations of muscle lactate were also found after  $\beta$ -blockade which thus indicates that the decreased lactate release is not due to less production of lactate but rather to a changed transport of lactate from the muscle cells to the perfusing blood.

A third mechanism for the impaired lactate diffusion could be altered recruitment of the muscle fibres which could alter the relationship between metabolism and perfusion in different areas in the muscles. In this context it can be mentioned that ethanol given intra venously has been shown to change the glycogen breakdown in different fibres with increased muscle lactate concentrations (9) which supports the concept of this as a possible mechanism also during beta-blockade.

The mechanism that regulates the normal increase in blood flow in exercising muscles has been discussed for several years. Local changes secondary to the increase in metabolic rate are generally believed to produce the increased flow. The results from this study with no difference in leg blood flow between the blocked and unblocked leg during submaximal exercise indicate that the vascular  $\beta_2$  receptors are not involved in the regulation of leg blood flow during a strenuous steady state exercise.

exercise test ( $p < 0.05$ ) In the leg blocked with propranolol the release decreased to 44 % of the preblocked value whereas the release in the control leg was unchanged (Fig 1b)

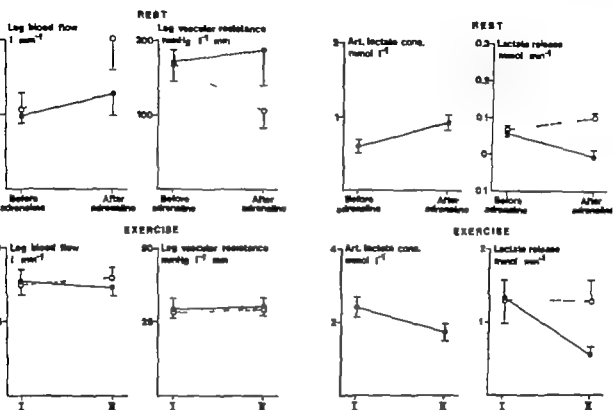


Figure 1

- a) Leg blood flow and leg vascular resistance at rest (before and after adrenaline) and during exercise (●—● test leg ○—○ control leg) Mean  $\pm$  SEM are indicated
- b) Arterial lactate concentration and lactate release at rest (before and after adrenaline) and during exercise (●—● test leg ○—○ control leg) Mean  $\pm$  SEM are indicated

## Discussion

The main finding in the present study is the marked decrease in lactate release from the leg after acute beta-adrenoreceptor blockade with a reduction by almost 50 % during exercise. No definite explanation for this can be given but it is worth noting that in the cat skeletal muscle a beta adrenergic dilatator response can be evoked during sympathetic stimulation (10). The neurogenic  $\beta$ -dilatation is confined to the small resistance vessels with little influence on total flow. Furthermore the latter study shows that the dilator response can be eliminated by propranolol, with a reduction of the transcapillary fluid absorption by 50 % and hence a reduction of the available capillary surface. This could explain the decrease in lactate release found in the present study as a result of a mass transport mechanism despite an unchanged total leg blood flow.

Another possible explanation for the reduced lactate release could however be a reduced glycogenolysis with less production of lactate. No measurement of muscle lactate was done in this study but earlier results both after acute propranolol treatment in dogs (11) and chronic treatment with alprenolol (4) have shown an increased glycogenolysis after  $\beta$ -blockade. Furthermore in the latter study higher concentrations of muscle lactate were also found after  $\beta$ -blockade which thus indicates that the decreased lactate release is not due to less production of lactate but rather to a changed transport of lactate from the muscle cells to the perfusing blood.

A third mechanism for the impaired lactate diffusion could be altered recruitment of the muscle fibres which could alter the relationship between metabolism and perfusion in different areas in the muscles. In this context it can be mentioned that ethanol given intra venously has been shown to change the glycogen breakdown in different fibres with increased muscle lactate concentrations (9) which supports the concept of this as a possible mechanism also during beta-blockade.

The mechanism that regulates the normal increase in blood flow in exercising muscles has been discussed for several years. Local changes secondary to the increase in metabolic rate are generally believed to produce the increased flow. The results from this study with no difference in leg blood flow between the blocked and unblocked leg during submaximal exercise indicate that the vascular  $\beta_2$  receptors are not involved in the regulation of leg blood flow during a strenuous steady state exercise.



## References

- 1 Brick I Glover W Hutchinson K & Roddie I Effects of propranolol on peripheral vessels in man *Am J Cardiol* 18 329 1966
- 2 Drabkin D L & Austin J H Spectrophotometric studies II Preparations from washed blood cells nitric oxide hemoglobin and sulfhemoglobin *J Biol Chem* 112 5 1935
- 3 Frisk Holmberg M Jorfeldt L & Juhlin Dannfeldt A Influence of longterm antihypertensive alprenolol treatment on hemodynamic and metabolic responses to prolonged exercise in man *Clin Pharm & Ther* 21 675 1977
- 4 Frisk-Holmberg M Jorfeldt L Juhlin Dannfeldt A & Karlsson J Effect of long term beta-blocking treatment on muscle metabolism in hypertensive man XV Nordiske Kongress för Fysiologi of Farmakologi 1976 121
- 5 Garby L & Vuille J C The amount of trapped plasma in a high speed microcapillary hematocrit centrifuge *Scand J Clin Lab Invest* 13 642 1961
- 6 Hohorst H J Kreutz F H & Bücher T H Über Metabolitgehalte und Metabolitkonzentrationen in der Leber der Ratte *Biochem Z* 18 332 1959
- 7 Johnsson G The effects of intra arterially administered propranolol and H56/28 on blood flow in the forearm - a comparative study of two beta adrenergic receptor antagonists *Acta Pharmacol Toxicol* 25 63 1967
- 8 Jorfeldt L & Wahren J Leg blood flow during exercise in man *Clin Sci* 41 459 1971
- 9 Juhlin Dannfeldt A Jorfeldt L Hagenfeldt L & Hultén B The influence of ethanol on free fatty acid and carbohydrate metabolism during exercise in man *Clin Sci Mol Med* 53 205 1977
- 10 Lundvall J & Jörhult J Beta adrenergic microvascular dilatation evoked by sympathetic stimulation *Acta Physiol Scand* 92 572 1974
- 11 Nazar K Brzezinska Z Lyszczarz J & Danielewicz Kotowicz A Sympathetic control of the utilization of energy substrates during long term exercise in dogs *Arch Intern Physiol Biochim* 79 873 1971
- 12 Trap-Jensen J Clausen J P Noer J Larsen C A Krogsgaard A R & Christensen N J The effect of beta adrenoceptor blockers on cardiac output liver blood flow and skeletal muscle blood flow in hypertensive patients *Acta Physiol Scand Suppl* 440 30 1976

### Hemodynamic effects of acute and long-term treatment with Labetalol

Lysbo Svendsen, T. Rasmussen, S. Nielsen, P. E. Hartling, O. and Trap-Jensen, J.

Department of Clinical Physiology Frederiksberg Hospital and Department of Internal Medicine C Diakonissestiftelsen, DK-2000 Frederiksberg, Denmark.

Labetalol is a new antihypertensive drug with competitive  $\alpha$  and  $\beta$  adrenoceptor-blocking properties (4). The ratio of the  $\alpha$ - and  $\beta$ -blocking effects is about 1:3 after oral administration. Like propranolol labetalol is unselective with respect to  $\beta_1$ - and  $\beta_2$ -receptors and it is without intrinsic sympathomimetic activity (9).

It has been suggested that a combination of  $\alpha$ - and  $\beta$  adrenoceptor blocking drugs should be ideal for lowering the blood pressure since the latter should block the reflex effects of the former when the peripheral resistance is lowered by vasodilatation (5).

The antihypertensive effect have been documented in several studies (2-8). In contrast with the adrenergic  $\beta$ -blocking agents labetalol can reduce the blood pressure acutely (10).

The purpose of this study was to evaluate the hemodynamic effects of labetalol after acute intravenous administration and after three months oral treatment in patients with essential hypertension.

#### Material and methods

The study comprised 10 patients (9 male and 1 female) with essential hypertension (WHO grade I-II) mean age 48 years range 34 to 61 years. All patients consented to participate in the study after being informed in details of its nature and purpose. Eight patients were untreated. Two patients had earlier been treated with diuretics. All the patients had at least four weeks placebo period before the first hemodynamic evaluation.

The cardiac output (CO) were determined by thermodilution technique using a Swan-Ganz thermodilution catheter and an Edwards cardiac output computer. The CO was given as an average of at least five determinations.

The blood pressure (BP) was measured sphygmomanometrically. The heart rate (HR) was registered continuously by three precordial leads. The tip of

a Swan-Ganz thermodilution catheter was placed in the pulmonary artery under fluoroscopic guidance. After one hour of supine rest the plasma half-life of Indocyanine green (ICG) was determined after an i.v. bolus injection of 12.5 mg ICG. In order to obtain an estimate of the splanchnic-hepatic blood flow. Hereafter control values for CO, BP and HR were measured in the supine position after five min., of standing and during the last two min. of supine bicycle exercise for six min. at 50 watt and 100 watt.

After one hours rest, labetalol was injected intravenously in a dose of 0.75 mg per kg b.w. 15 min. later the above described study was repeated using exactly the same protocol.

After three month oral treatment with labetalol 1-200 mg orally daily the hemodynamic studies were repeated in five patients as described for the control study.

### Results:

In the acute study the results are based on ten patients whereas the results in the long-term study at this moment are based on five reexamined patients. Both systolic and diastolic BP were reduced significantly after labetalol both in the acute and in the long-term study (see fig. 1).

The mean values for the mean BP (mmHg  $\pm$  1 SEM) was in the control study  $138 \pm 2.7$  in the supine position,  $136 \pm 2.8$  after five min. standing,  $144 \pm 2.0$  after six min. of exercise at 50 watt and  $152 \pm 2.4$  after six min. exercise at 100 watt. After acute i.v. administration of labetalol the corresponding values for mean BP were:  $119 \pm 2.9$ ,  $113 \pm 4.6$ ,  $129 \pm 4.1$  and  $136 \pm 4.4$  respectively. After three month oral treatment with labetalol the corresponding values for mean BP were:  $120 \pm 3.1$ ,  $116 \pm 4.9$ ,  $128 \pm 1.7$  and  $137 \pm 4.8$  respectively.

Cardiac Index was unchanged at rest supine after five min. standing and during six min. of supine exercise at 50 watt as well after acute as after long-term treatment with labetalol.

Cardiac Index decreased significantly during exercise at 100 watt. The mean values (l per min. per m<sup>2</sup>) being  $7.1 \pm 1.3$  in the control study,  $6.0 \pm 0.2$  after i.v. administration and  $6.4 \pm 0.1$  after three month oral treatment.

There was a significant decrease in total peripheral resistance in the supine and upright position both after acute and long-term treatment.

During the two exercise periods the total peripheral resistance was unchanged after labetalol. The HR was unchanged in the supine position after

acute administration of labetalol but reduced significantly by 6 per cent after long term treatment. Both after acute and long term treatment HR was reduced by 5 to 12 per cent after five min, standing and during exercise at 50 watt and 100 watt. The reduction in HR was most pronounced during exercise at 100 watt. The stroke index was significantly increased in the upine position both in the acute and in the long-term study but no significant changes were seen in the upright position and during exercise. There was not observed any significant changes in the half life of ICG after labetalol. This is taken to indicate that splanchnic-hepatic blood flow was unchanged.

### Discussion

The significant reduction in BP both after acute and oral administration of labetalol confirms that labetalol is an effective antihypertensive drug. The unchanged cardiac index in the upine position and the reduction during exercise in the acute study is in accordance with the results of Koch (6). In the upright position however we have not found any significant changes in cardiac index. This contrast to the findings of Koch (6) who found a significant reduction of about 18 per cent in this position. The changes in cardiac index in the long term study are in accordance with the result found by Edwards and Rafferty (3) and by Metha and Cohn (7).

The only difference between the acute and long-term hemodynamic effects of labetalol found here is the reduction in HR seen only after long-term treatment. This is in accordance with the findings of Koch (6). Other investigators have reported a decrease in HR of 7 beats per min, after i.v. injection of 50 mg labetalol (10). This discrepancy may be ascribed to differences in the resting sympathetic tone as judged by the pretreatment HR. The hemodynamic effects of labetalol differs markedly from those of propranolol. The most striking differences are the acute reduction in BP, the unchanged cardiac index, rest and during standing and the unchanged splanchnic-hepatic blood flow. These differences may in all likelihood be ascribed to the adrenoreceptor-blocking properties of labetalol.

At rest labetalol reduces the peripheral vascular resistance both acutely and after three month or 1 treatment. This is taken to indicate that the vasodilator or adrenoreceptor-blocking effect is present for a longer period of time.

Thus from a hemodynamic point of view labetalol is an active antihypertensive drug.

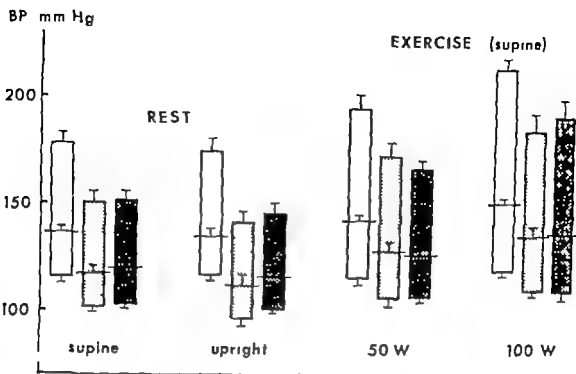


Fig 1 Systolic- mean- and diastolic-blood pressure, mean values  $\pm$  1 SEM, before (open bars) after acute (light hatched bars) and during long-term oral treatment (dark hatched bars)

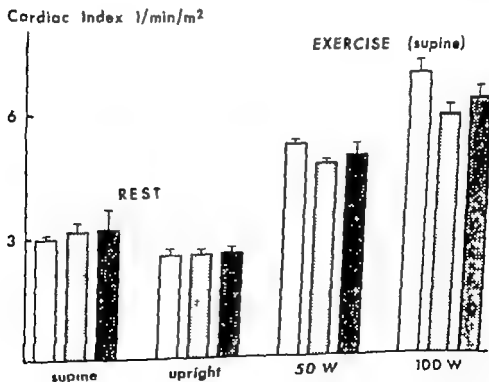


Fig 2 The cardiac index during supine rest when standing and during supine exercise at 50 and 100 watt. Symbols as in Fig 1

## References

1. Dingle H, J Dollery C T, Daniel J. Labetalol in resistant hypertension. Br J clin. Pharmac. Suppl 3 751 (1976)
2. Dent R, K Ilaway G S M, A pilot trial of labetalol (AH 5158 A) A combined alpha and beta blocker in the treatment of hypertension. N. Z. Med. J. 86, 213 (1977)
3. Edwards R, C Raftery E B. Haemodynamic effects of long-term oral labetalol. Br J clin. Pharmac. Suppl 3 733 (1976)
4. Farmer J B, Kennedy I, Levy G P, Marshall R, J. Pharmacology of AH 5158 a drug which blocks both  $\alpha$ - and  $\beta$ -adrenoceptors. Br J Pharmac. 45, 660 (1972)
5. Glimore E, Wall J, Chidsey C T. Treatment of essential hypertension with a new vasodilator in combination with beta-adrenergic blockade. New Engl J Med 282, 531 (1970)
6. Koch G. Acute hemodynamic effects of an alpha and beta-receptor blocking agent (AH 5158) on the systemic and pulmonary circulation at rest and during exercise in hypertensive patients. Amer Heart J 93, 585 (1977)
7. Mathis J C, Cohn J N. Hemodynamic effects of labetalol an alpha and beta adrenergic blocking agent in hypertensive subjects. Circulation 55, 370 (1977)
8. Prichard B N, Boskes A, J. Labetalol in long-term treatment of hypertension. Br J Clin. Pharmac. Suppl 3 743 (1976)
9. Richards D A, Tuckman J, Prichard B N, C. Assessment of  $\alpha$ - and  $\beta$ -adrenoceptor blocking actions of labetalol. Br J clin. Pharmac. 3, 849 (1976)
10. Rønne-Rasmussen J Ø, Andersen G S, Jensen N, B, Anderson E. Acute effect of intravenous labetalol in the treatment of systemic arterial hypertension. Br J clin. Pharmac. Suppl 3 805 (1976)

# HEMODYNAMIC LONG-TERM EFFECTS OF LABETALOL IN ESSENTIAL HYPERTENSION

Per Lund-Johansen

Medical Department A University of Bergen School of  
Medicine 5016 Bergen Norway

## INTRODUCTION

From a hemodynamic point of view antihypertensive drugs being able to reduce total peripheral resistance would seem to be of particular interest since this is increased in most patients with established hypertension (6) Labetalol possesses both alpha- and beta-adrenergic blocking properties (1 13) and short term (3 4) and a few long-term (5 2) hemodynamic studies in hypertensive patients have suggested a reduction in total peripheral resistance by this compound

This paper is a short report of the effects of labetalol on central hemodynamics at rest and during exercise in subjects with moderate essential hypertension before and after one year on treatment The full paper including studies of plasma concentrations of labetalol will be published elsewhere (12)

## MATERIAL AND METHODS

The study included 15 men mean age 47.5 years with untreated essential hypertension in WHO stage I The hemodynamic study was performed with subjects resting (supine and sitting) and during exercise at 50 100 and 150 Watt Intraarterial blood

pressure was recorded continuously by a catheter in the brachial artery. Heart rate was recorded by ECG. Cardiac output by dye dilution method (Cardiogreen) and oxygen consumption by Douglas bag and micro Scholander method (6)

Labetalol was given as tablets twice daily 200-800 mg/day (mean dose 450 mg/day). Two subjects almost syncope when sitting in the ergometer chair after the 150 W load at the restudy. No other serious side effects were seen.

## RESULTS

The casual blood pressure dropped in all subjects. The mean values from 167/110 to 134/88 mmHg.

The major hemodynamic changes are shown in fig. 1. The oxygen consumption did not show significant changes. The heart rate decreased significantly at rest (18%) and during exercise (19%). The stroke volume was unchanged at rest sitting but increased significantly at rest supine and during exercise (8%). Thus the cardiac index decreased less than the heart rate at rest supine only 7% (not significant). At rest sitting the decrease was 17% (significant) and during exercise 11% (significant). The intraarterial pressure decreased considerably about 23% at rest and 21% during exercise. All changes highly significant. Ten of 15 patients became normotensive (BP 140/90 mmHg at rest sitting). The total peripheral resistance decreased in most patients. The mean decrease was 19% (significant) at rest supine and 13% (significant) during exercise. At rest sitting the decrease was less 11% (not significant).



# HEMODYNAMIC LONG-TERM EFFECTS OF LABETALOL IN ESSENTIAL HYPERTENSION

Per Lund-Johansen

Medical Department A University of Bergen School of  
Medicine 5016 Bergen Norway

## INTRODUCTION

From a hemodynamic point of view antihypertensive drugs being able to reduce total peripheral resistance would seem to be of particular interest since this is increased in most patients with established hypertension (6). Labetalol possesses both alpha- and beta-adrenergic blocking properties (1-13) and short term (3-4) and a few long-term (5-2) hemodynamic studies in hypertensive patients have suggested a reduction in total peripheral resistance by this compound.

This paper is a short report of the effects of labetalol on central hemodynamics at rest and during exercise in subjects with moderate essential hypertension before and after one year on treatment. The full paper including studies of plasma concentrations of labetalol will be published elsewhere (12).

## MATERIAL AND METHODS

The study included 15 men mean age 47.5 years with untreated essential hypertension in WHO stage I. The hemodynamic study was performed with subjects resting (supine and sitting) and during exercise at 50, 100 and 150 Watt. Intraarterial blood

in similar patients. The results resemble those seen after long term therapy with the combination of prazosin and a beta blocker (11) and agree well with what should be expected from a drug with both alpha and beta adrenergic blocking properties. The reduction in blood flow is clearly less than what is seen by the use of beta blockers alone and the reduction in total peripheral resistance is significant.

# LABELALOL 15

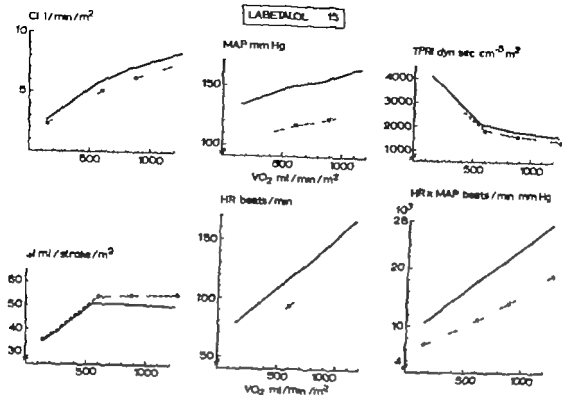


Figure 1 Mean (n=15) hemodynamic changes at rest sitting and during exercise before — and during ----- treatment with labetalol CI = cardiac index MAP = mean arterial pressure TPRI = total peripheral resistance index SI = stroke index HR = heart rate

## DISCUSSION

Labetalol was a very effective antihypertensive drug in these patients with moderate essential hypertension. The pressure reduction was obtained through a combination of decrease in total peripheral resistance and in cardiac output. This hemodynamic profile differs from what is seen by the use of thiazide diuretics (7) beta-blockers (9, 10) or prazosin (8).

LABETALOL IN THE TREATMENT OF SEVERE ESSENTIAL HYPERTENSION: RELATIONSHIP BETWEEN ARTERIAL BLOOD PRESSURE, PLASMA CATECHOLAMINES, PLASMA RENIN ACTIVITY, PLASMA ALDOSTERONE AND BODY WEIGHT.

H J Kornerup E B Pedersen M J Christensen A Pedersen & G Pedersen Department of Medicine C and M Århus Kommunehospital and Århus University and Department of Internal Medicine and Endocrinology Herlev Hospital Copenhagen Denmark

INTRODUCTION

In the majority of patients with essential hypertension the sympathetic nervous activity is normal (7 8) and recently it has been suggested that the renin system activity declines with progression of essential hypertension except in the malignant phase (12) During antihypertensive therapy however blood pressure (BP) regulation may be influenced by alterations in the activities of the sympathetic nervous system and the renin system (1 3 10)

In the present study the interrelationships between BP the sympathetic nervous activity the renin-aldosterone system and sodium and fluid balance - as judged by alterations in body weight (BW) - were assessed in patients with severe essential hypertension during combined alpha- and beta-adrenergic receptor blockade induced by oral labetalol treatment

MATERIAL AND METHODS

Twelve patients with severe essential hypertension (WHO stage 2-3) 10 males and 2 females aged 32-67 years were included in the study Before the study 8 patients had received oral diazoxide therapy during several months and the remaining 4 were candidates for oral diazoxide therapy because of resistance to conventional antihypertensive treatment

All antihypertensive agents except furosemide were gradually discontinued during several weeks before the study while the patients were controlled in the out-patient clinic Furosemide in a dosage of 80-250 mg/d was then continued throughout the study period in the same dosage in each patient After treatment with furosemide as the only drug for 2 weeks labetalol was given in increasing dosages from 300 to 1200-2400 mg/d divided in 3 doses

# REFERENCES

- 1 Brittain R T & Levy G P A review of the animal pharmacology of labetalol a combined alpha- and beta-adrenoceptor blocking drug Brit J clin Pharmac Suppl 681 1976
- 2 Edwards R C & Raftery E B Haemodynamic effects of long-term oral labetalol Brit J clin Pharmac Suppl 733 1976
- 3 Joekes A M & Thompson F D Acute haemodynamic effects of labetalol and its subsequent use as an oral hypotensive agent Brit J clin Pharmac Suppl 789 1976
- 4 Koch G Haemodynamic effects of combined alpha- and beta-adrenoceptor blockade after intravenous labetalol in hypertensive patients at rest and during exercise Brit J clin Pharmac Suppl 725 1976
- 5 Koch G Combined alpha- and beta-adrenoceptor blockade with oral labetalol in hypertensive patients with reference to haemodynamic effects at rest and during exercise Brit J clin Pharmac Suppl 729 1976
- 6 Lund-Johansen P Hemodynamics in early essential hypertension Acta Med Scand Suppl 482 1 1967
- 7 Lund-Johansen P Hemodynamic changes in long-term diuretic therapy of essential hypertension Acta Med Scand 187 509 1970
- 8 Lund-Johansen P Haemodynamic changes at rest and during exercise in long-term prazosin therapy of essential hypertension In Prazosin - Evaluation of a new antihypertensive agent (ed D W K Cotton) p 43 Excerpta Medica Amsterdam 1974
- 9 Lund-Johansen P Haemodynamic long-term effects of a new beta-adrenoceptor blocking drug atenolol (ICI 66082) in essential hypertension Brit J clin Pharmac 3 445 1976
- 10 Lund-Johansen P Hemodynamic long term effects of timolol at rest and during exercise in essential hypertension Acta Med Scand 199 263 1976
- 11 Lund-Johansen P Haemodynamic long-term effects of prazosin plus tolamolol in essential hypertension Brit J clin Pharmac 4 141 1977
- 12 Lund-Johansen P & Bakke O M Hemodynamic effects and plasma concentration of labetalol during long-term treatment of essential hypertension Brit J clin Pharmac In press
- 13 Richards D A Pharmacological effects of labetalol in man Brit J clin Pharmac Suppl 721 1976

not changed further after treatment for 2 months. PA and blood glucose concentration did not change significantly during treatment with labetalol.

#### Renin-aldosterone system

Before treatment with labetalol PRA and PAC values were normal or slightly elevated probably due to furosemide treatment. No differences in pretreatment values of PRA and PAC were present between patients in whom BP did not respond to labetalol alone and those in whom BP responded to labetalol. The changes in PRA and PAC during treatment with labetalol varied greatly. Thus PRA decreased by 19-53% in 6, increased by 51-118% in 4 and remained unchanged in 2 patients, and PAC decreased by 34-47% in 5, increased by 91-192% in 3 and remained unchanged in 4 patients. The changes in mean values of PRA and PAC during treatment with labetalol were not significant. Labetalol induced a slight but significant increase in plasma potassium concentration from 3.3 to 3.6 mEq/l ( $p < 0.05$ ).

#### Relationship between the variables studied

No correlation was found between the basal values of the variables in study. Changes ( $\Delta$ ) in the variables after 2 months of treatment with labetalol, however, disclosed some significant correlations. Thus  $\Delta$ BW correlated closely and inversely to  $\Delta$ PMA ( $\rho = -0.82$ ,  $p < 0.01$ ) and to  $\Delta$ PRA ( $\rho = -0.75$ ,  $p < 0.01$ ). Also  $\Delta$ mean BP correlated inversely to  $\Delta$ PRA ( $\rho = -0.63$ ,  $p < 0.05$ ) and to  $\Delta$ PAC ( $\rho = -0.61$ ,  $p < 0.05$ ). Furthermore  $\Delta$ PRA correlated positively to  $\Delta$ PMA ( $\rho = 0.82$ ,  $p < 0.01$ ) and to  $\Delta$ PAC ( $\rho = 0.66$ ,  $p < 0.05$ ). Finally a negative correlation between  $\Delta$ mean BP and  $\Delta$ PMA ( $\rho = -0.58$ ,  $0.10 > p > 0.05$ ) and a positive correlation between  $\Delta$ mean BP and  $\Delta$ BW ( $\rho = 0.50$ ,  $p > 0.10$ ) were at a borderline level of significance.

#### DISCUSSION

The present study indicates that combined alpha- and beta-adrenergic receptor blockade induced by labetalol may provide an adequate control of BP in patients with severe essential hypertension.

Contrasting to the expected increase in PMA during an alpha- and beta-adrenergic receptor blockade (3), labetalol in the present study induced a decrease in PMA. This might, however, be caused by interference of the sympathetic nervous activity by sodium and fluid retention indicated to occur by a significant in-

month and this treatment was continued unchanged during the second month. In 5 patients BP was not reduced and labetalol was supplemented with hydralazine 75-200 mg/d divided in 3 daily dosages during the third month.

Blood samples for measurements of plasma noradrenaline concentration (PNA), plasma adrenaline concentration (PA), plasma renin activity (PRA) and plasma aldosterone concentration (PAC) were collected by an indwelling peripheral venous catheter at 9 00 a.m. after recumbence for one hour and an 8-hour fast just before start of treatment with labetalol and every month during the next 2 or 3 months. No dietary restrictions were prescribed. Plasma catecholamines were determined by a sensitive double-isotope derivative technique (2). PRA was measured as described by Giese & al. (5) and PAC was measured according to the method of Damkjer Nielsen (11). BP measured by sphygmomanometry and pulse rate were determined after one hour in the supine position and after 2 minutes in the upright position. In association with the BP readings BW was measured.

## RESULTS

The results are summarized in table I.

### Blood pressure and pulse rate

Labetalol and furosemide - in 5 patients supplemented with hydralazine - reduced average supine BP from 214/140 to 173/112 mmHg and average upright BP from 208/139 to 152/105 mmHg ( $p < 0.01$ ). The decreases in average supine and average upright pulse rate during treatment with labetalol were significant ( $p < 0.01$ ).

### Body weight

The increase in mean BW from 77.9 to 80.3 kg during treatment with labetalol was significant ( $p < 0.01$ ).

### Plasma catecholamines

Before treatment with labetalol values of PNA and PA were normal or slightly elevated probably due to furosemide treatment. No differences in pretreatment values of PNA or PA were present between patients in whom BP was unresponsive to labetalol and those in whom BP responded to labetalol. Labetalol induced a significant fall in the mean value of PNA from 0.30 to 0.15 ng/ml during treatment for one month ( $p < 0.05$ ) which was

Table shows values  $\pm$ SD of supine and upright BP (mean) supine and upright pulse rate (per minute) BP (mm) PRA (ng/ml) (ng/ml PRA (ng Ang I/100 ml/h) AC ng/100 ml plasma potassium concentration, (mmol/l) and blood urea concentration (mg/100 ml before (A) and during treatment with labetalol for one week (B), for 2 months (C) and for 2 months following patients on additional treatment (D).

Supine BP	114/71	$\pm 6/4$	121/70	$\pm 6/7$	121/71	$\pm 6/4$	121/71	$\pm 6/7$
Upright BP	100/130	$\pm 6/4$	68/71	$\pm 7$	68/110	$\pm 6/5$	62/130	$\pm 6/7$
Supine pulse rate			77	$\pm 7$	78	$\pm 7$	77	$\pm 7$
Upright pulse rate	80		77		78	$\pm 7$	77	
HR	77	$\pm 4$	76	$\pm 4$	79	$\pm 4$	80	$\pm 4$
PRA	20 $\pm$ 0.05		21 $\pm$ 0		20 $\pm$ 0		20 $\pm$ 0	0.1
PA	85 $\pm$ 0	81	85 $\pm$ 0		87 $\pm$ 0	81	11 $\pm$ 0	
PR	70 $\pm$ 0	75	77 $\pm$ 0	75	1.70 $\pm$ 0	01	08 $\pm$ 0	15 $\pm$ 0
PC	10	2	2		23	$\pm 0.5$	1	$\pm 1$
Plasma potassium	3.0		3.0		3.0			
Blood glucose	85				81	$\pm 0$		

Values only for patients on labetalol and hydrochloride



crease in mean BW during treatment with labetalol. Thus  $\Delta BW$  correlated inversely with  $\Delta PNA$  which suggests that PNA decreased in those patients with sodium and fluid retention contrasting to those without sodium and fluid retention in accordance with an inverse relationship between sympathetic nervous activity and sodium.

Also sodium and fluid retention might have modified renin release during treatment with labetalol. This was indicated by a negative correlation between  $\Delta BW$  and  $\Delta PRA$  which suggests that renin release was suppressed in those patients with sodium and fluid retention contrasting to those without retention of sodium and fluid in accordance with the wellknown inverse relationship between renin and sodium. A pronounced increase in PRA occurred in some of our patients during treatment with labetalol despite the presence of a beta-adrenergic receptor blockade which usually suppresses renin release (169). According to the baroreceptor-theory (4) a decrease in BP might have contributed to the stimulatory effect on renin release in these patients supported by the findings of a negative correlation between  $\Delta \text{mean BP}$  and  $\Delta PRA$ .

The positive correlation between  $\Delta PNA$  and  $\Delta PRA$  found in the present study was probably due to a common action of alteration in sodium and fluid balance upon renin and catecholamine release since the renal sympathetic innervation conceivably was blocked by labetalol.

Lack of a correlation between  $\Delta PAC$  and  $\Delta BW$  suggests that other hitherto unidentified mechanisms than hyperaldosteronism are involved in sodium and fluid retention associated with labetalol treatment.

In conclusion: the present study suggests that labetalol through its combined alpha- and beta-adrenoreceptor-blocking action induces important alterations in the state of sodium and fluid balance which affect renin as well as sympathetic nervous activity whereby the antihypertensive effect of labetalol may be modified. Further investigations by direct measurements of body sodium and fluid content instead of BW are necessary to verify such a hypothesis.



crease in mean BW during treatment with labetalol. Thus  $\Delta BW$  correlated inversely with  $\Delta PNA$  which suggests that PNA decreased in those patients with sodium and fluid retention contrasting to those without sodium and fluid retention in accordance with an inverse relationship between sympathetic nervous activity and sodium.

Also sodium and fluid retention might have modified renin release during treatment with labetalol. This was indicated by a negative correlation between  $\Delta BW$  and  $\Delta PRA$  which suggests that renin release was suppressed in those patients with sodium and fluid retention contrasting to those without retention of sodium and fluid in accordance with the wellknown inverse relationship between renin and sodium. A pronounced increase in PRA occurred in some of our patients during treatment with labetalol despite the presence of a beta-adrenergic receptor blockade which usually suppresses renin release (169). According to the baroreceptor-theory (4) a decrease in BP might have contributed to the stimulatory effect on renin release in these patients supported by the findings of a negative correlation between  $\Delta \text{mean BP}$  and  $\Delta PRA$ .

The positive correlation between  $\Delta PNA$  and  $\Delta PRA$  found in the present study was probably due to a common action of alteration in sodium and fluid balance upon renin and catecholamine release since the renal sympathetic innervation conceivably was blocked by labetalol.

Lack of a correlation between  $\Delta PAC$  and  $\Delta BW$  suggests that other hitherto unidentified mechanisms than hyperaldosteronism are involved in sodium and fluid retention associated with labetalol treatment.

In conclusion the present study suggests that labetalol through its combined alpha- and beta-adrenoreceptor-blocking action induces important alterations in the state of sodium and fluid balance which affect renin as well as sympathetic nervous activity whereby the antihypertensive effect of labetalol may be modified. Further investigations by direct measurements of body sodium and fluid content instead of BW are necessary to verify such a hypothesis.

Tabl Mean values  $\pm$  SEM of supine and upright BP, body supine and upright pulse rate (per minute),  
 24 Day PKA (ng/ml) Pz (ng/ml) PMA (ng/kg I/100 ml/h) PNC (ng/100 ml) plasma potassium concentration,  
 body/L and blood lactate concentration (ng/100 ml) before (A) and during treatment with labeled (for one  
 month (T), for 2 weeks (P) and for 2 weeks (lactate) relative to additional hydration (H).

Supine BP	214/1	$\pm 6/$	1/120	$\pm 0/2$	151/11	$\pm 0/4$	/1	6/3
Upright BP	200/139	$\pm 6/$	100/11	/5	91/11	$\pm 0/4$	12/105	1/3
Supine pulse rate	83	$\pm$		$\pm$	70		73	
Upright pulse rate	80	$\pm$	77				77	
24	77	$\pm 4$	79	$\pm 4$	73	$\pm 4$	80	$\pm 4$
PKA		10 $\pm 0$ 03		0.21 $\pm 0$ 03		20 $\pm 0$		20 $\pm 0$ 04 <sup>1</sup>
Pz		80 $\pm 0$ 01		80 $\pm 0$ 03		87 $\pm 0$ 01		11 $\pm 0$ 1 <sup>1</sup>
PMA		1.70 $\pm 0$ 35		37 $\pm 0$ 25		$\pm 0$ 41		06 $\pm 0$ 15 <sup>1</sup>
AC		20		-8 $\pm$		21. $\pm$ -8		1. $\pm$ 4 <sup>1</sup>
Plasma potassium		$\pm 0$		$\pm 0$		$\pm 0$		
Blood glucose		89		11		81		

Values only from patients on labeled and hydration.

# REFERENCES

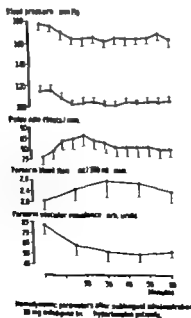
- 1 Buhler, F R Laragh J H Baer L Vaughan E D & Brunner H R : Propranolol inhibition of renin secretion New Engl J Med 287 1209 1972
- 2 Christensen N J Plasma noradrenaline and adrenaline in patients with thyreotoxicosis and myxoedema Clin Sci Mol Med 45:163 1973
- 3 Christensen N J Trap-Jensen J Svendsen T L , Rasmussen E & Nielsen P E : Effects of labetalol on plasma noradrenaline and adrenaline in hypertensive man Submitted for publication
- 4 Davis J O : The control of renin release Am J Med 55:333 1973
- 5 Glese J Jørgensen M Nielsen M D Lund, J O & Munck O : Plasma renin concentration measured by use of radioimmunoassay for angiotensin I Scand J Clin Lab Invest 26: 355 1970
- 6 Hansson L : Beta-adrenergic blockade in essential hypertension Acta Med Scand Suppl 550:1 1973
- 7 Lake C R Kopin I J Sieglar M G & Coleman M D Plasma catecholamines and neurogenic hypertension New Engl J Med 297:53 1977
- 8 Pedersen E B & Christensen N J : Catecholamines in plasma and urine in patients with essential hypertension determined by double-isotope derivative techniques Acta Med Scand 198:373 1975
- 9 Pedersen E B & Kornerup H J : Plasma renin concentration in essential hypertension during beta-adrenergic blockade and vasodilator therapy Europ J Clin Pharmacol 12:93 1977
- 10 Pettinger W A & Keeton R : Altered renin release and propranolol potentiation of vasodilatory drug hypotension J Clin Lab Invest 55:236 1975
- 11 Rask-Madsen J Bruusgaard A Munck O Nielsen M D & Worming E : The significance of bile acids and aldosterone for the electrical hyperpolarization of human rectum in obese patients treated with intestinal bypass operation Scand J Gastroent 9:417 1974
- 12 Shalekamp M A D H Krauss X H Kolsters G Shalekamp M P A & Birkenhager W H : Renin suppression in hypertension in relation to body fluid volumes patterns of sodium excretion and renal haemodynamics Clin Sci Mol Med 45 1:283 1973

EFFECTS OF NIFEDIPINE ON BLOOD PRESSURE, REGIONAL HEMODYNAMICS,  
PLASMA RESIN ACTIVITY AND PLASMA CATECHOLAMINES IN PATIENTS WITH  
ARTERIAL HYPERTENSION.

■ Lederballe Pedersen E Mikkelsen H J Kornerup & N N Christensen  
From Department of Clinical Pharmacology University of Aarhus  
DK 8000 Aarhus C Denmark

The calcium antagonists nifedipine (Adalat<sup>R</sup> BAY a 1040) and verapamil (Isoptin<sup>R</sup>), which were introduced for the treatment of angina pectoris both have a marked effect on the excitation-contraction coupling in vascular smooth muscle (Grün & Fleckenstein 1972). The relaxant effects of these drugs in isolated human vessels have been demonstrated (Mikkelsen et al 1978 a 1978 b). Previous clinical investigations of verapamil as a vasodilator in man indicated that calcium antagonists might be useful in the treatment of arterial hypertension (Lederballe Pedersen 1978). This necessitated a pilot study of nifedipine as an antihypertensive agent.

Eleven patients with essential hypertension of varying severity received a test dose of 10 mg nifedipine by the sublingual route. The figure below illustrates the effects on blood pressure, heart rate, forearm blood flow and calculated forearm vascular resistance.



## REFERENCES

- 1 Buhler F R Laragh J H , Baer L Vaughan E D & Brunner, H R Propranolol inhibition of renin secretion *New Engl J Med* 287:1209 1972
- 2 Christensen N J Plasma noradrenaline and adrenaline in patients with thyreotoxicosis and myxoedema *Clin Sci Mol Med* 45 163 1973
- 3 Christensen N J Trap-Jensen J Svendsen T L Rasmussen S & Nielsen P E Effects of labetalol on plasma noradrenaline and adrenaline in hypertensive man Submitted for publication
- 4 Davis J O : The control of renin release *Am J Med* 55:333 1973
- 5 Giese J Jørgensen M Nielsen M D Lund J O & Munck O : Plasma renin concentration measured by use of radioimmunoassay for angiotensin I *Scand J Clin Lab Invest* 26: 355 1970
- 6 Hansson L Beta-adrenergic blockade in essential hypertension *Acta Med Scand Suppl* 550:1 1973
- 7 Lake, C R Kopin I J , Ziegler M ■ & Coleman M D : Plasma catecholamines and neurogenic hypertension *New Engl J Med* 297:53 1977
- 8 Pedersen E B & Christensen N J : Catecholamines in plasma and urine in patients with essential hypertension determined by double-isotope derivative techniques *Acta Med Scand* 198:373 1975
- 9 Pedersen E B & Kornerup H J : Plasma renin concentration in essential hypertension during beta-adrenergic blockade and vasodilator therapy *Europ J Clin Pharmacol* 12:93 1977
- 10 Pettinger, W A & Keeton K : Altered renin release and propranolol potentiation of vasodilatory drug hypotension *J Clin Lab Invest* 55:236 1975
- 11 Rask-Madsen J Bruusgaard A Munck O Nielsen M D & Worming H : The significance of bile acids and aldosterone for the electrical hyperpolarization of human rectum in obese patients treated with intestinal bypass operation *Scand J Gastroent* 9:417 1974
- 12 Shalekamp M A ■ H Krauss X H Kolsters ■ Shalekamp M D A & Birkenhager W H : Renin suppression in hypertension in relation to body fluid volumes patterns of sodium excretion and renal haemodynamics *Clin Sci Mol Med* 45 Suppl 1:223- 1973

In contrast to previous experiences with other potent vasodilators a significant fall in body weight was found Plasma renin activity showed an insignificant increase from  $1.20 \pm 0.27$  to  $1.80 \pm 0.54$  ng/80% ml/h after 6 weeks of therapy Side effects in the form of heat sensations in face and limbs was noted in several patients during the first days of treatment Although the side effects tended to vanish after some days they limited the daily dosage in a few of the patients

The results of the present study of nifedipine as an anti-hypertensive agent leaves us with the picture of a powerful vasodilator with a prompt effect on blood pressure An increase in sympathetic activity manifested by rise in pulse rate plasma noradrenaline and plasma renin activity was found and in consequence of this combined therapy with a betablocking agent might be beneficial Studies of this aspect are in progress

#### References

- Grün G & A Fleckenstein: *Arzneim Forsch* 1972 22:334-344  
Lederballe Pedersen O *Europ J clin Pharmacol* 1978 In press  
Mikkelsen E X-E Andersson & B Bengtsson *Acta Pharmacol Toxicol* 1978 a:42 14-22  
Mikkelsen E X-E Andersson & O Lederballe Pedersen: 1978 b  
In preparation

Reprint requests to O Lederball Pedersen  
Department of Clinical Pharmacology  
University of Aarhus  
DK-8000 Aarhus C  
Denmark



A significant drop in blood pressure and a concomitant rise in pulse rate occurred already after 10 minutes. Forearm blood flow rose to maximal values after 30 minutes whereas the calculated vascular resistance reached nadir levels 45 minutes after the administration of nifedipine. The decrease in blood pressure lasted for several hours.

Plasma concentrations of nifedipine were determined by a fluorometric method<sup>(+)</sup>. A few patients had peak concentrations of nearly 200 ng/ml after only 15-30 minutes but most patients showed a slower absorption with maximum values of about 50 ng/ml after 90 minutes. There was a close correlation between the plasma concentrations of nifedipine and the decrease in calculated vascular resistance (at  $t = 45$  min:  $r = 0.86$   $p < 0.02$   $n = 7$ ). The obtained decrease in blood pressure was not significantly correlated to the plasma concentration of nifedipine.

After the acute administration of 10-20 mg of nifedipine there was a rapid rise in plasma renin activity from a mean of  $1.40 \pm 0.33$  ng/80% ml/h at  $t = 0$  min to  $2.10 \pm 0.51$  at  $t = 60$  min ( $p < 0.005$   $n = 10$ ). Plasma noradrenaline also showed a rise from  $0.25 \pm 0.03$  to  $0.47 \pm 0.05$  ng/ml ( $p < 0.01$   $n = 6$ ) whereas no change was observed in the adrenaline values. The increase in plasma renin activity significantly correlated with the basal values ( $r = 0.94$   $p < 0.001$   $n = 10$ ). No significant correlation was present between the increase in plasma renin activity and the rise in plasma noradrenaline.

The effects of continued oral treatment with nifedipine was evaluated in a group of 10 hypertensive patients who received 30-60 mg daily for 6 weeks. Resting supine blood pressure was reduced from a mean value of  $175/115 \pm 6/2$  to  $151/96 \pm 4/3$  mm Hg ( $p < 0.001$ ). Mean pulse rate increased from  $82 \pm 2$  to  $91 \pm 4$  beats/min ( $p < 0.02$ ). Forearm blood flow was not significantly higher at the end of therapy than before but the calculated forearm vascular resistance showed a significant decrease during therapy.

(+) Plasma determinations of nifedipine were kindly carried out by Dr. Rönisch, Bayer AG, Leverkusen, Germany.

(3 women) participated. They were informed of the aim of the study and gave their written consent. After investigation at the Hypertension Clinic they were classified as having an essential hypertension corresponding to WHO stage I-II. The blood pressure was expressed as mean arterial pressure.<sup>5</sup> It was based on 3 separate ambulant pressure recordings: the group mean value was  $117 \pm 5$  mm Hg. The mean age was  $46 \pm 5$  years. 20% of the patients belonged to the low renin group according to their fasting plasma renin activity/24 hr urine sodium excretion index. The investigation was performed with the patients supine. An intravenous cannula was inserted in both forearms: one for injection and one for sampling. Clonidine was given as bolus injections in doses from 75 to 275  $\mu$ g. 9 patients received 2 doses at separate occasions. Heart frequency and blood pressure was measured non-invasively by the same person with a mercury sphygmomanometer every 15 min the hr before the injection and according to a pre-determined protocol during 24 hrs after the injection as described.<sup>3</sup> Venous sample for clonidine determinations were drawn in connection with the pressure recordings. Concentration time data for each subject were then treated with a digital computer program (NONLIN) to find the best fit of a polyexponential equation. All values were weighted and given as mean  $\pm$  S.D. as described.<sup>3</sup>

SHR experiments Blood pressure was registered from an catheter in the s. carotis on awake SHR. Through an indwelling catheter in v. jugularis clonidine was infused at different rates to achieve steady state plasma concentration between 0.5-10 ng/ml as described.<sup>4</sup> 5-6 rats were studied at each

RELATIONSHIP BETWEEN CLONIDINE KINETICS AND ITS BLOOD  
PRESSURE EFFECTS

Marianne Frisk-Holmberg

Lennart Paalzow

Section Clin Pharm Medical School Dept Pharmacol Pharm  
BMC and Hypertension Clinic University Hospital Uppsala  
University S-751 23 Uppsala Sweden

Clonidine in daily doses from 0.075-1.2 mg is used in Scandinavia for the treatment of essential hypertension. Higher doses are used elsewhere and during chronic administration with approximately 5.4 mg daily giving peak plasma concentrations ~20 ng/ml the therapeutic response was abolished<sup>7</sup>. Davies et al<sup>1</sup> studying healthy volunteers have also reported that the blood pressure lowering effect is reduced when higher plasma concentrations of clonidine are present. After bolus doses of 0.15-0.3 mg a hypertensive response has been observed in man<sup>5</sup>. Higher doses give a more pronounced blood pressure increase. These studies indicate a concentration dependence of clonidine's blood pressure effects. The aim of the present investigation was to study relationship between clonidine kinetics and the therapeutic response in essential hypertensives after bolus injections. To study the concentration dependence of the blood pressure effects during steady state conditions the spontaneous hypertensive rat (SHR) was investigated.

PATIENTS AND METHODS

13 previously untreated healthy patients of both sexes

(3 women) participated. They were informed of the aim of the study and gave their written consent. After investigation at the Hypertension Clinic they were classified as having an essential hypertension corresponding to WHO stage I-II. The blood pressure was expressed as mean arterial pressure<sup>6</sup>. It was based on 3 separate ambulant pressure recordings: the group mean value was  $117 \pm 5$  mm Hg. The mean age was  $46 \pm 5$  years. 20% of the patients belonged to the low renin group according to their fasting plasma renin activity/24 hr urine sodium excretion index. The investigation was performed with the patients supine. An intravenous cannula was inserted in both forearms: one for injection and one for sampling. Clonidine was given as bolus injections in doses from 75 to 275 µg. 9 patients received 2 doses at separate occasions. Heart frequency and blood pressure was measured non-invasively by the same person with a mercury sphygmomanometer every 15 min the hr before the injection and according to a pre-determined protocol during 24 hrs after the injection as described<sup>3</sup>. Venous samples for clonidine determinations were drawn in connection with the pressure recordings. Concentration-time data for each subject were then treated with a digital computer program (MONLIN) to find the best fit of a polyexponential equation. All values were weighted and given as mean  $\pm$  S.E. as described<sup>3</sup>.

SHR experiments Blood pressure was registered from an catheter in the  $\alpha$  carotis on awake SHR. Through an indwelling catheter in v. jugularis clonidine was infused at different rates to achieve steady state plasma concentration between 0.5-10 ng/ml as described<sup>4</sup>. 5-6 rats were studied at each

RELATIONSHIP BETWEEN CLONIDINE KINETICS AND ITS BLOOD  
PRESSURE EFFECTS

Marianne Frisk-Holmberg

Lennart Paalzow

Section Clin Pharm Medical School Dept Pharmacol Pharm  
BMC and Hypertension Clinic University Hospital Uppsala  
University S-751 23 Uppsala Sweden

Clonidine in daily doses from 0.075-1.2 mg is used in Scandinavia for the treatment of essential hypertension. Higher doses are used elsewhere and during chronic administration with approximately 5.4 mg daily giving peak plasma concentrations ~20 ng/ml the therapeutic response was abolished<sup>7</sup>. Davies et al<sup>1</sup> studying healthy volunteers have also reported that the blood pressure lowering effect is reduced when higher plasma concentrations of clonidine are present. After bolus doses of 0.15-0.3 mg a hypertensive response has been observed in man<sup>5</sup>. Higher doses give a more pronounced blood pressure increase. These studies indicate a concentration dependence of clonidine's blood pressure effects. The aim of the present investigation was to study relationship between clonidine kinetics and the therapeutic response in essential hypertensives after bolus injections. To study the concentration dependence of the blood pressure effects during steady state conditions the spontaneous hypertensive rat (SHR) was investigated.

PATIENTS AND METHODS

13 previously untreated healthy patients of both sexes

between the patients plasma renin status and the blood pressure effect. The blood pressure reduction was also significantly correlated to the logarithm of the plasma concentration of clonidine ( $r=0.86$   $p=0.01$ ). Concentrations above  $0.2$  ng/ml gave a significant blood pressure decrease. After doses of  $0.2-0.275$  mg the blood pressure reduction was still present at the 24 hrs observation. A positive correlation was also found between clonidine plasma concentrations and the blood pressure reduction all observation points starting after the distribution phase (Fig. 1) when an apparent pseudoequilibrium is achieved ( $r=0.89$   $p=0.02$ ).

#### Relationship clonidine steady state concentrations ( $C_{pss}$ ) and blood pressure effects (SHR)

$C_{pss}$  concentrations of  $0.5$  ng/ml gave a significant reduction of mean arterial blood pressure  $5 \pm 2$  mm Hg ( $p < 0.05$ ;  $n=5$ ). The blood pressure reduction was linearly related to the  $C_{pss}$  of clonidine up to levels of  $2 \pm$  ng/ml. Above that level the blood pressure reducing effect of clonidine was attenuated and at levels of  $8.0$  and  $10$  ng/ml a blood pressure increase was seen. These animal data indicate that clonidine has a narrow plasma concentration range for its blood pressure reducing effect.

#### DISCUSSION

The present data show that after i.v. bolus of clonidine there is a significant correlation between the therapeutic effect and the plasma concentration of clonidine at all observation points when an apparent pseudoequilibrium of the drug is achieved. The pharmacokinetics of clonidine show that

steady state level. Venous sampling for clonidine analysis were drawn. Values are mean  $\pm$  S D

Clonidine was determined in plasma with a gas liquid chromatographic method using an electron-capture detector [1]

### RESULTS

Clonidine kinetics After bolus i.v. doses (0.075-0.275 mg) the plasma concentration time curves displayed a biexponential decay during 0-1440 min. The kinetics of clonidine was described by an open 2-compartment model. The half-life for the  $\alpha$ -phase varied between 2.4-15.1 min and for the  $\beta$ -phase between 7.4-11.4 hrs. No significant difference between the half-lives after the different doses was found but the decay of both the  $\alpha$ -phase and the  $\beta$ -phase was decreased after the highest dose (0.275 mg). The apparent volume of the distribution ( $VD_{\beta}$ ) was 3.29 l/kg and unaffected by dose. A gradual increase in the area under the plasma concentration curve was observed between the 0.075-0.2 mg ( $256.22 \pm 44$  min/ml) and the highest dose 0.275 mg (386 min/ml). The mean plasma clearance was 4 ml/min/kg (0.075-0.2 mg) and was lower after the 0.275 mg dose (2.98 ml/min/kg).

### Relationship clonidine kinetics and therapeutic response

Clonidine gave a dose-dependent blood pressure reduction. The blood pressure decrease was significantly correlated to the logarithm of the dose ( $r=0.975$   $p<0.001$ ) from the 0.075 mg dose to 0.275 mg. The dose-response curve was steep. The mean arterial blood pressure reduction was  $38 \pm 5.29$  mm Hg after the highest dose. The heart rate was also reduced but the relationship was not significant. No relationship was found

# REFERENCES

- 1 Davies, D S , Wing, L M , Reid, I L , Neill, P  
Tippett, P , Dollery, C G Pharmacokinetics and concentration effect relationships of intravenous and oral clonidine  
Clin Pharm Ther 1977 21 593-601
- 2 Edlund, I O , Paalzow, L Quantitative gas liquid chromatographic determination of clonidine in plasma Acta pharmacol toxicol 1977 40 145-152
- 3 Frisk-Holmberg, M , Edlund, P O , Paalzow, L Relationship between clonidine kinetics and its therapeutic effect  
Br J Clin Pharmacol 1978 in press
- 4 Frisk Holmberg, M , Gunnarsson, C , Paalzow, L Concentration dependence of the blood pressure effects of clonidine  
J Pharm Pharmacol to be published
- 5 Kroetz, F , McRaven, H , Kioschos, I M , Kirkenwall, W M  
The acute effects of catapresan cardiac hemodynamics of hypertensive man in Catapres in hypertension Ed M E Conolly Butterworth London pp 39-69
- 6 Rasbemer, R F In Cardiovascular dynamics 2nd ed  
W B Saunders Co Ltd Philadelphia and London 1968  
p 343
- 7 Wing, L M H , Reid, I L , Davies, D S , Dargie, H J  
Dollery, C.T Apparent resistance to the hypotensive effect of clonidine Brit Med J 1977 1 136-138



the volume of distribution is high and the mean plasma clearance is 4 ml/min/kg. The half-life of the terminal plasma concentration curve between 7-11 hrs and after single doses of 0.10 mg or more blood pressure lowering plasma concentrations of clonidine are still present 12 hrs after the administration. This fact would allow a 2 dose regimen.

During steady state conditions in the SHR, clonidine has a narrow plasma concentration range for its blood pressure lowering effect indicating a therapeutic window. This observation could be one explanation for the therapeutic variability and inefficiency of the drug in the clinical situation.

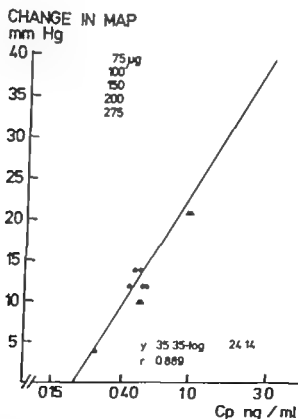


Figure legend

Relationship between reduction of mean blood pressure (MAP) mean value of individual values and mean plasma clonidine concentration (Cp) for doses of 0.075-0.275 mg (log scale)

During the first four weeks of active therapy the doses of metoprolol alprenolol and oxprenolol were 100 mg b i d 200 mg b i d and 80 mg b i d respectively During the following eight weeks all patients received respective  $\beta$ -blocker in the double dose These doses of the three  $\beta$ -blockers were regarded as equipotent with regard to reduction of exercise induced tachycardia and are the doses generally recommended in the treatment of hypertension (2) After this dose-finding period the patients were followed up for another 38 weeks with control visits after 12 and 26 weeks respectively During this follow-up period the patients were maintained on the lowest dose giving normotension i e a blood pressure  $<160/95$  mm Hg Patients not satisfactorily controlled on the highest dose were given hydrochlorothiazide 12.5 mg b i d in addition At each control visit systolic and diastolic blood pressure and heart rate were recorded in the sitting position after 5 minutes rest Unwanted effects were recorded according to a check-list

The following laboratory investigations were carried out after 6 weeks on placebo and subsequently after 12 and 50 weeks on active therapy serum creatinine bilirubin alkaline phosphatase B-GOT B-GPT chole terol triglycerides uric acid and A N F

### Results

Of the 106 patients who entered the study 91 completed the fi st 3 months on active therapy and 71 patients completed the whole study Only two of the 35 drop-outs were withdrawn due to possible ide-effects of treatment with  $\beta$ -blockers (see under heading Side-effects)

A comparison between metoprolol, alprenolol and oxprenolol  
in the treatment of hypertension

- A double-blind study over 12 months -

- By Jaakko Tuomilehto -  
North Karelia Project  
University of Kuopio  
Finland

Introduction:

Metoprolol is a  $\beta_1$ -selective  $\beta$ -blocker devoid of intrinsic stimulating activity (I S A ) and alprenolol and oxprenolol are two non-selective  $\beta$ -blockers with I S A (1) With the background of these pharmacological differences we undertook the following comparative study between the three  $\beta$ -blockers in order to evaluate their antihypertensive effect and tolerability

Patients and methods

106 patients with a newly discovered and previously untreated hypertension were included into the study There were 94 males and 12 females with a mean age of 42 years range 16 - 68 years All patients belonged to WHO-stage I or II Patients with AV-block chronic obstructive lung diseases cardiac decompensation and insulin treated diabetes mellitus were primarily excluded from this investigation

The design of the study is given in figure 1

After the initial six weeks run-in period on placebo patients with a sitting BP  $\geq 160/96$  mm Hg were randomly allocated to one of three parallel groups to be treated with either metoprolol alprenolol or oxprenolol

Compared to placebo all these reductions of the heart rate were statistically significant. No significant differences were found between the three  $\beta$  blocker with regard to the reduction of the heart rate.

#### B) Follow-up period

In the subsequent long-term follow-up period up to 12 months the patients were maintained on the lowest effective dose-level of each  $\beta$ -blocker and if necessary hydrochlorothiazide 12.5 mg b.i.d. was added. When comparing the three groups with regard to heart rate and blood pressure after this period no differences were found. The three groups differed however with regard to dose-level of respective  $\beta$ -blocker and also with regard to the number of patients requiring addition of hydrochlorothiazide (HCT).

Of the 20 patients in the metoprolol group 5 were satisfactorily controlled on 200 mg daily, 14 on 400 mg daily and only 1 patient needed HCT in addition. Of the 25 patients in the alprenolol group 2 patients were satisfactorily controlled on 400 mg daily, 15 on 800 mg daily and 8 patients needed HCT in addition. In addition one patient in this group was withdrawn from the study due to poor blood pressure control on alprenolol 800 mg daily. Of the 26 patients in the oxprenolol group 2 patients were satisfactorily controlled on 160 mg daily, 10 on 320 mg daily and the remaining 14 patients required HCT in addition.

# 1 Effects on blood pressure and heart rate (Table I)

## A) Dose-finding period

The average blood pressure at the end of the run-in period on placebo was 162/104 164/102 and 163/104 mm Hg in the metoprolol alprenolol and oxprenolol groups respectively

After 4 weeks on the lower dose-level the reduction amounted to 18/10 18/5 and 13/6 mm Hg compared to placebo after metoprolol alprenolol and oxprenolol respectively. These reductions of the blood pressure were statistically significant compared to placebo for all three  $\beta$ -blockers. After additional 8 weeks on the higher dose-level the corresponding reductions were 23/14 22/8 and 16/8 mm compared to placebo.

When comparing the three  $\beta$ -blockers no differences were found with regard to blood pressure on the lower dose-level. However on the higher dose-level metoprolol caused a significantly more pronounced reduction of the diastolic blood pressure than alprenolol ( $p < 0.05$ ) and oxprenolol ( $p < 0.05$ ).

The heart rate on placebo was 75 79 and 78 beats/min in the metoprolol alprenolol and oxprenolol groups respectively. After 4 weeks on the lower dose-level the reduction amounted to 7 6 and 8 beats/min and after 12 weeks on the higher dose-level to 14 12 and 10 beats/min on metoprolol alprenolol and oxprenolol respectively.

Compared to placebo all these reductions of the heart rate were statistically significant. No significant differences were found between the three  $\beta$ -blockers with regard to the reduction of the heart rate.

#### B) Follow-up period

In the subsequent long-term follow up period up to 12 months the patients were maintained on the lowest effective dose-level of each  $\beta$ -blocker and if necessary hydrochlorothiazide 12.5 mg b i d was added. When comparing the three groups with regard to heart rate and blood pressure after this period no differences were found. The three groups differed however with regard to dose-level of respective  $\beta$ -blocker and also with regard to the number of patients requiring addition of hydrochlorothiazide (HCT).

Of the 20 patients in the metoprolol group 5 were satisfactorily controlled on 200 mg daily, 14 on 400 mg daily and only 1 patient needed HCT in addition. Of the 25 patients in the alprenolol group 2 patients were satisfactorily controlled on 400 mg daily, 15 on 800 mg daily and 8 patients needed HCT in addition. In addition one patient in this group was withdrawn from the study due to poor blood pressure control on alprenolol 800 mg daily. Of the 26 patients in the oxprenolol group 2 patients were satisfactorily controlled on 160 mg daily, 10 on 320 mg daily and the remaining 14 patients required HCT in addition.

Metoprolol monotherapy gave a satisfactory blood pressure control in 95% of the patients. The corresponding effect was achieved in 68% and 46% of the patients in the alprenolol and oxprenolol groups respectively.

## 2 Side-effects

The frequency of side-effects was low on all three  $\beta$ -blockers. A slight increase was seen on the higher dose-level compared to the lower dose-level. One patient was withdrawn during treatment with metoprolol due to insomnia in connection with high alcohol consumption and another during alprenolol treatment due to dizziness and tiredness.

## 3 Laboratory investigations after 12 months compared to placebo

The three  $\beta$ -blockers did not cause any significant changes of serum creatinine, triglycerides and A N F. A minor but statistically significant reduction of serum cholesterol was seen in the metoprolol and oxprenolol groups which might be due to dietary advice. Serum bilirubin increased after treatment in each group being significant for metoprolol and oxprenolol. Serum uric acid was significantly increased in the alprenolol and oxprenolol groups where addition of HCT was more common than in the metoprolol group. No clinical symptoms associated with these changes were found.

## Conclusion:

In view of the findings in this study metoprolol appears to be more effective than alprenolol and oxprenolol in reducing the diastolic blood pressure when compared in doses regarded as

equipotent with regard to  $\beta_1$ -blockade. The number of patients requiring addition of other antihypertensive agents were also fewer on metoprolol than on alprenolol and oxprenolol. Another non selective  $\beta$ -blocker, pindolol, which has a high I S A, has also been found to be a less potent anti-hypertensive agent than metoprolol (3). No differences were found between the  $\beta$ -blockers with regard to tolerability during this long-term study ranging over one year.



Table Reduction of load pressure and heart rate compared to baseline

	Loadline	Low dose	High dose	Hydrochlorothiazide or equivalent with NCT
<b>Fixed dose group (500 mg)</b>				
Metoprolol	1/104	8/1	2/1	23/1
Alprenolol	164/182	8/5	22/9 or 8/10	26/18
Oxprenolol	1/104	13/5	7/9 or 8/10	23/1
<b>Fixed dose group (500 mg)</b>				
Metoprolol	70			19
Alprenolol	70		III	
Oxprenolol	70			19

III not significant compared to metoprolol  
 <II compared to metoprolol



Metoprolol monotherapy gave a satisfactory blood pressure control in 95% of the patients. The corresponding effect was achieved in 68% and 46% of the patients in the alprenolol and oxprenolol groups respectively.

## 2 Side-effects

The frequency of side-effects was low on all three  $\beta$ -blockers. A slight increase was seen on the higher dose-level compared to the lower dose-level. One patient was withdrawn during treatment with metoprolol due to insomnia in connection with high alcohol consumption and another during alprenolol treatment due to dizziness and tiredness.

## 3 Laboratory investigations after 12 months compared to placebo

The three  $\beta$ -blockers did not cause any significant changes of serum creatinine, triglycerides and A M F. A minor but statistically significant reduction of serum cholesterol was seen in the metoprolol and oxprenolol groups which might be due to dietary advice. Serum bilirubin increased after treatment in each group being significant for metoprolol and oxprenolol. Serum uric acid was significantly increased in the alprenolol and oxprenolol groups where addition of HCT was more common than in the metoprolol group. No clinical symptoms associated with these changes were found.

## Conclusion

In view of the findings in this study metoprolol appears to be more effective than alprenolol and oxprenolol in reducing the diastolic blood pressure when compared in doses regarded as

equipotent with regard to  $\beta_1$ -blockade. The number of patients requiring addition of other antihypertensive agents were also fewer on metoprolol than on alprenolol and oxprenolol. Another non-selective  $\beta$ -blocker, pindolol, which has a high I S A, has also been found to be a less potent anti-hypertensive agent than metoprolol (3). No differences were found between the  $\beta$ -blockers with regard to tolerability during this long-term study ranging over one year.



Table Reduction of blood pressure and heart rate compared to baseline mean values

	Low dose	Low dose	High dose	Randomisation or double-blind with MCT
<b>Fixed-dose regimen (mg/day)</b>				
Metoprolol	183/184	18/1	22/1	1/14
Alprenolol	64/182	18/8	22/8 (n.s.)	26/18
Oxprenolol	1/ 84	13/8	18/8 (n.s.)	22/18
<b>Flexi-dose regimen (mg/day)</b>				
Metoprolol	75			18
Alprenolol	78		12	18
Oxprenolol	78			18

n.s. not significant compared to metoprolol  
n.s. compared to metoprolol

## REFERENCES

- 1 Imhof P R      Characterization of beta-blockers as antihypertensive agents in the light of human-pharmacology studies    In    Beta-Blockers - Present Status and Future Prospects    (Ed : W Schweizer)    Hans Huber Publishers    Berne    40-46    1974
- 2 Ablad B    Ljung B    Sannerstedt R : Haemodynamic effects of  $\beta$ -adrenoceptor blockers in hypertension    Drugs 11 (Suppl 1)    127-134    1976
- 3 Tuomilehto J      A comparison between metoprolol and pindolol in the treatment of essential hypertension    Ann Clin Res 1978    in press

## HISTAMINERGIC AND RELATED MECHANISMS IN THE CENTRAL CONTROL OF BLOOD PRESSURE

Hari Peakkari, Heikki Karppanen and Pirkko Peakkari

*From the Department of Pharmacology, University of Oulu,  
SF-90220 Oulu 22, Finland*

Histamine is a putative neurotransmitter in the brain (16). The presence of histamine receptors of both the  $H_1$  and  $H_2$ -classes in the brain has been demonstrated (2) but their physiological significance is not clear.

It has been shown that the antihypertensive drug clonidine (2-[2,6-dichlorophenyl-iso]-2-imidazoline hydrochloride) is able to stimulate histamine  $H_2$ -receptors both in peripheral tissues (5, 11, 18) and in the brain (1, 9, 10, 12, 15). The administration of the specific histamine  $H_1$ -receptor antagonists mepyramide (8, 9, 10, 12) or cimetidine (6) intracerebroventricularly antagonises the hypotensive effect of clonidine in urethane-anesthetized rats. This suggests that cerebral histamine  $H_2$ -receptors may mediate the hypotensive effect of clonidine. Moreover, mepyramide alone raises the blood pressure (9). This finding implies that central histamine  $H_2$ -receptors are tonically activated in the anesthetized rat and contribute toward lowering of the blood pressure (9).

The theory of the role of central histamine  $H_1$ -receptors in the control of blood pressure and in the mediation of the hypotensive effect of clonidine is based on studies which indicate that mepyramide is a very specific blocker of the histamine  $H_1$ -receptors (3, 4). No other significant pharmacological effect of mepyramide has been demonstrated for the present. Since the central hypotensive effect of clonidine has been attributed to stimulation of central sympatho-inhibitory  $\alpha$ -adrenoceptors (21), the ability of mepyramide to block such receptors was studied. The role of histaminergic or related mechanisms in the central control of blood pressure was studied further by using known histamine receptor agonists and antagonists as well as the histamine-related agent imidazole acetic acid.

### MATERIALS AND METHODS

Male Sprague-Dawley rats (250–300 g) were anesthetized with urethane (1.5 g/kg intraperitoneally). The trachea was cannulated with a polyethylene tube and the rats were allowed to breathe spontaneously. The mean blood pressure was measured directly from the left femoral artery by means of a pressure transducer. The rats were placed in a stereotaxic instrument and an injection needle introduced into the lateral cerebral ventricle. A polyethylene catheter filled with the solution to be infused was attached to the needle. The required amount of solution was allowed to flow slowly by means of hydrostatic pressure. At the end of each experiment, methylene blue was injected and the proper position of the needle in the cerebral ventricle was ascertained.

The following drugs were used: Histamine dihydrochloride (Koch-Light Laboratories Ltd), diphenhydramine hydrochloride (Parke-Davis & Co.), imidazole acetic acid (Sigma Chemical Company). Mepyramide and dimespiz were kindly supplied by Dr. D.A.A. Owen of Smith Kline and French Laboratories Ltd.  $\alpha$ -Methylnoradrenaline was donated by Sterling-Winthrop. The doses of the drugs refer to the salt.

## REFERENCES

- 1 Imhof P R : Characterization of beta-blockers as antihypertensive agents in the light of human-pharmacology studies In Beta-Blockers - Present Status and Future Prospects (Ed : W Schweizer) Hans Huber Publishers Berne 40-46 1974
- 2 Ablad B Ljung B Sannerstedt R : Haemodynamic effects of  $\beta$ -adrenoceptor blockers in hypertension Drugs 11 (Suppl 1) 127-134 1976
- 3 Tuomilehto J : A comparison between metoprolol and pindolol in the treatment of essential hypertension Ann Clin Res 1978 in press

## HISTAMINERGIC AND RELATED MECHANISMS IN THE CENTRAL CONTROL OF BLOOD PRESSURE

Ileri Paakkari, Heikki Karppanen and Pirkko Pesäke

*From the Department of Pharmacology, University of Oulu  
SF-90220 Oulu 22, Finland*

Histamine is a putative neurotransmitter in the brain (16). The presence of histamine receptors of both the  $H_1$  and  $H_2$ -classes in the brain has been demonstrated (2) but their physiological significance is not clear.

It has been shown that the antihypertensive drug clonidine [2-(2,6-dichlorophenyl-amino)-2-imidazoline hydrochloride] is able to stimulate histamine  $H_2$ -receptors both in peripheral tissues (5, 11, 18) and in the brain (1, 9, 10, 12, 15). The administration of the specific histamine  $H_2$ -receptor antagonists metiamide (6, 9, 10, 12) or cimetidine (8) intracarotidobasally antagonises the hypotensive effect of clonidine in urethane-anesthetized rats. This suggests that cerebral histamine  $H_2$ -receptors may mediate the hypotensive effect of clonidine. Moreover, metiamide alone raises the blood pressure (9). This finding implies that central histamine  $H_2$ -receptors are tonically activated in the anesthetized rat and contribute toward lowering of the blood pressure (9).

The theory of the role of central histamine  $H_2$ -receptors in the control of blood pressure and in the mediation of the hypotensive effect of clonidine is based on studies which indicate that metiamide is a very specific blocker of the histamine  $H_2$ -receptors (3, 4). No other significant pharmacological effect of metiamide has been demonstrated for the present. Since the central hypotensive effect of clonidine has been attributed to a stimulation of central sympatho-inhibitory  $\alpha$ -adrenoceptors (21) the ability of metiamide to block such receptors was studied. The role of histaminergic or related mechanisms in the central control of blood pressure was studied further by using known histamine receptor agonists and antagonists as well as the histamine-related agent imidazole acetic acid.

### MATERIALS AND METHODS

Male Sprague-Dawley rats (260–300 g) were anesthetized with urethane (1.5 g/kg intraperitoneally). The trachea was cannulated with a polyethylene tube and the rats were allowed to breathe spontaneously. The mean blood pressure was measured directly from the left femoral artery by means of a pressure transducer. The rats were placed in a stereotaxic instrument and an injection needle introduced into the lateral cerebral ventricle. A polyethylene catheter filled with the solution to be infused was attached to the needle. The required amount of solution was allowed to flow slowly by means of hydrostatic pressure. At the end of each experiment, methylene blue was injected and the proper position of the needle in the cerebral ventricle was ascertained.

The following drugs were used: Histamine diphosphate (Koch-Light Laboratories Ltd), diphenhydramine hydrochloride (Parke-Davis & Co.), imidazole acetic acid (Sigma Chemical Company). Metiamide and dimepril were kindly supplied by Dr. D.A.A. Owen of Smith, Kline and French Laboratories Ltd.  $\alpha$ -Methylnoradrenaline was donated by Sterling-Winthrop. The doses of the drugs refer to the salt.

## RESULTS AND DISCUSSION

The administration of histamine the natural activator of both  $H_1$ - and  $H_2$ -receptors into the lateral cerebral ventricle (l.c.v.) induced a dose related rise in blood pressure (Fig. 1). The histamine  $H_1$ -receptor blocking drug diphenhydramine (100 or 200  $\mu$ g l.c.v.) antagonised the hypertensive effect of centrally administered histamine (Fig. 1). This confirms the earlier report that the central hypertensive effect of histamine is due to the stimulation of histamine  $H_1$  receptors (7).

The possible existence of sympatho-inhibitory histamine  $H_2$ -receptors was studied by using the selective histamine  $H_2$ -receptor agonist dimaprit (13). The administration of dimaprit l.c.v. at the doses of 5–80  $\mu$ g per rat elevated the blood pressure in a dose-related manner. At the dose of 80  $\mu$ g the rise in blood pressure was 21 mm Hg in comparison with the saline treated control group ( $p < 0.01$ ). However this effect of dimaprit was not antagonised by metiamide pretreatment (11 mg l.c.v.). This finding suggests that the hypertensive effect of dimaprit may be due to some other property of the drug than the stimulation of histamine  $H_2$ -receptors. It has been shown that dimaprit is an inhibitor of the histamine catabolising enzymes (17). Further studies are needed to elucidate the mechanism of the central hypertensive effect of dimaprit.

The central hypertensive effect of metiamide (9) and the antagonism of the clonidine-

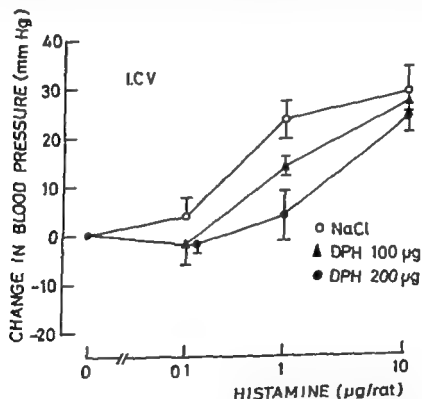


Fig. 1 Effect of intracerebroventricular administration of histamine on blood pressure in urethane-anesthetized rats. Increasing doses of histamine were administered into the lateral cerebral ventricle at 30-min intervals. The maximal rise in blood pressure after each dose was used in the calculation of the results. Diphenhydramine hydrochloride 100  $\mu$ g ( $\Delta$ ) or 200  $\mu$ g ( $\bullet$ ) intracerebroventricularly was given 30 min before the start of histamine administration. Control rats ( $\circ$ ) received saline instead of diphenhydramine. The difference between the control and diphenhydramine (200  $\mu$ g) groups was significant at the  $p < 0.01$  level at the histamine dose of 1  $\mu$ g. The number of rats was 7 in each group. Vertical bars indicate s.e.

induced hypotension by the specific histamine  $H_2$ -receptor blocking drugs (6 9 10 12) suggest the presence of sympatho-inhibitory histamine  $H_1$ -receptors in the brain while the hypertensive effects of histamine and dimaprit do not support this view. Since some  $\alpha$ -adrenoceptor blocking drugs antagonise the hypotensive effect of clonidine (21) the ability of metiamide to block central sympatho-inhibitory  $\alpha$ -adrenoceptors was studied by using  $\alpha$ -methylnoradrenaline ( $\alpha$ -MNA) an established agonist of central  $\alpha$ -receptors (21). While  $\alpha$ -adrenoceptor blocking drugs antagonise the central hypotensive effect of  $\alpha$ -MNA (21) metiamide pretreatment (488  $\mu$ g i.c.v.) clearly potentiated the  $\alpha$ -MNA induced fall in blood pressure. At the dose of 20  $\mu$ g,  $\alpha$ -MNA lowered the blood pressure on the average by 10 % in the control rats and by 30 % in the metiamide pretreated rats. The difference between the groups is significant at the  $p < 0.01$  level. At the  $\alpha$ -MNA dose of 80  $\mu$ g the fall in blood pressure was 15 % in the control rats and 40 % in the metiamide-pretreated rats ( $p < 0.01$ ). Therefore it can be concluded that metiamide does not block the sympatho-inhibitory  $\alpha$ -adrenoceptors in the brain. Moreover since metiamide pretreatment antagonises the hypotensive effect of clonidine but potentiates the hypotensive effect of  $\alpha$ -MNA, it can hardly be maintained (21) that clonidine and  $\alpha$ -MNA have the same mechanism of action in the central nervous system.

The failure of histamine to mimic the central hypotensive effect of clonidine suggests that metiamide and clonidine are able to affect in the brain some mechanism which is related to but not identical with histamine  $H_2$ -receptors. It has been shown that imidazole acetic acid which is a metabolite of histamine (20) and can also be formed via a transamination pathway from histidine (14 20) lowers the blood pressure in cats upon intracerebroventricular administration (19) in the urethane-anaesthetised rats imidazole acetic acid (30–390  $\mu$ g i.c.v.) induced a dose-related fall in blood pressure. Metiamide (11 mg i.c.v.) significantly antagonised the hypotensive effect of imidazole acetic acid. At the dose of 390  $\mu$ g the fall in blood pressure was approximately 50 % in the control group and about 30 % in the metiamide group. In this respect the central hypotensive effect of imidazole acetic acid mimics that of clonidine.

It is premature to implicate a new class of cerebral receptors in the hypotensive effects of clonidine and imidazole acetic acid. However the present results could be explained conveniently by imagining the existence of cerebral sympatho-inhibitory "imidazole receptors". An activation of these receptors would bring about a lowering of blood pressure. The hypertensive effect of metiamide could be explained by the blockade of tonically activated "imidazole receptors". The blockade of these receptors by metiamide might, in turn, imply that they are closely related to histamine  $H_1$ -receptors. According to the present hypothesis imidazole acetic acid would lower blood pressure by acting as a natural activator of the sympatho-inhibitory "imidazole receptors". The synthetic antihypertensive imidazoline compound clonidine would also be able to activate these receptors.

The hypothesis of the role of histamine  $H_1$  and  $H_2$ -receptors as well as that of the "imidazole receptors" in the central control of blood pressure is summarised in Fig. 2. It should be emphasized that further studies are needed to elucidate the mechanisms by which imidazole acetic acid and clonidine lower the blood pressure and by which metiamide antagonises their effect. The concept presented here can only be used as a working hypothesis. In addition, since the histamine  $H_2$ -receptor agonist dimaprit appears to exert non-specific hypertensive effects, the cerebral  $H_1$ -receptors may in fact mediate hypotensive effects.



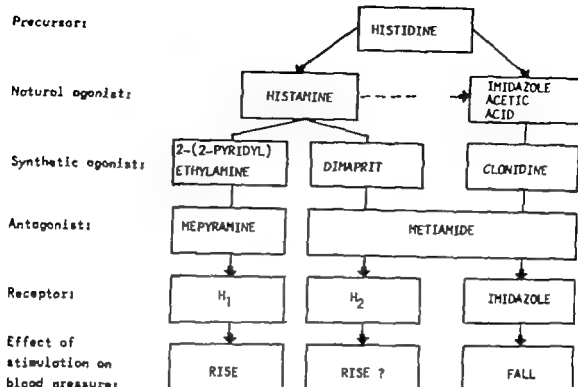


Fig. 2. Hypothesis of the role of histamine H<sub>1</sub> and H<sub>2</sub>-receptors, and "imidazole receptors" in the central control of blood pressure. For further explanation, see the text.

### ACKNOWLEDGEMENTS

This work was done under a contract with the Association of Finnish Life Insurance Companies. It was also partly supported by a grant from the Paavo Nurmi Foundation. The skilful technical assistance of Mrs. Sirpa Rytönen, Miss Tiina Heikkinen and Miss Eila Pesonen is gratefully acknowledged. We are much obliged to Mrs. Leena Pyykkö and Mrs. Helena Saari for their efficient secretarial assistance.

### REFERENCES

1. Audigier Y, Virion A. & Schwartz J.-C. Stimulation of cerebral histamine H<sub>2</sub> receptors by clonidine. *Nature* 262: 307, 1976.
2. Baudry M, Martres M.P. & Schwartz, J.-C. H<sub>1</sub> and H<sub>2</sub>-receptors in the histamine induced accumulation of cyclic AMP in guinea-pig brain slices. *Nature* 263: 362, 1976.
3. Black J.W., Duncan W.A.M., Emmett, J.C., Ganeflin C.R., Hesselbo T., Parsons M.E. & Wyllie J.H. Metamide — an orally active histamine H<sub>2</sub>-receptor antagonist. *Agents Actions* 3: 133, 1973.
4. Brimblecombe R.W., Duncan W.A.M., Owen D.A.A. & Parsons M.E. The pharmacology of burinamide and metamide, two histamine H<sub>2</sub>-receptor antagonists. *Feder. Proc.* 35: 1931, 1976.

- 5 Csörgödy A. & Kobinger W. Investigations into the positive inotropic effect of clonidine in isolated hearts. *Naunyn-Schmiedeberg's Arch Pharmacol.* 262 123 1974
- 6 Finch L., Harvey C.A., Hicks, P.E. & Owen D.A.A.. Clonidine-induced hypotension. Further evidence for a central interaction with histamine H<sub>2</sub> receptor antagonists in the rat. *Neuropharmacol.*, in press.
- 7 Finch L. & Hicks, P.E. The cardiovascular effects of intraventricularly administered histamine in the anaesthetized rat. *Naunyn-Schmiedeberg's Arch Pharmacol.* 293 161 1978
- 8 Henning, M. & Rubenson, A.. Evidence that the hypotensive action of methyllopa is mediated by central actions of methylnoradrenaline. *J Pharm. Pharmacol.* 23 407 1971
- 9 Karppinen, H. Paakkari, I. & Paakkari, P. Further evidence for central histamine H<sub>2</sub> receptor involvement in the hypotensive effect of clonidine in the rat. *Europ J. Pharmacol.* 42 209 1977
- 10 Karppinen H. Paakkari, I. Paakkari P. Huotari, R. & Orma A.—L. Possible involvement of central histamine H<sub>2</sub>-receptors in the hypotensive effect of clonidine. *Nature* 269 587 1976.
- 11 Karppinen H.O. & Westermann, E. Increased production of cyclic AMP in gastric tissue by stimulation of histamine H<sub>2</sub>-receptors. *Naunyn-Schmiedeberg's Arch Pharmacol.* 279 83 1978.
12. Paakkari I. Karppinen, H. & Paakkari P. Site and mode of action of clonidine in the central nervous system. *Acta Med Scand Suppl.* 602 106 1976
- 13 Parsons, M.E., Owen, D.A.A., Ganettin C.R. & Durant G.J. Dimaprit — [5-[3-(N,N-dimethylemino)propyl]isothiourea] — a highly specific histamine H<sub>2</sub>-receptor agonist. Part 1. *Pharmacology Agents Actions* 7 31 1977
- 14 Robinson, J.D. & Green, J.P. Presence of imidazoleacetic acid riboside and ribotide in rat tissues. *Nature* 203. 1178 1964
15. Sestry B.S. & Phillips, J.W. Evidence that clonidine can activate histamine H<sub>2</sub> receptors in rat cerebral cortex. *Neuropharmacol.* 17 223, 1977
- 16 Schwartz, J.-C. Histaminergic mechanisms in brain. *Ann Rev Pharmacol Toxicol.* 17 325 1977
- 17 Shaff R.E. & Beaven, M.A. Inhibition of histamine-N-methyltransferase and histamine (diamine oxidase) by a new histamine H<sub>2</sub>-receptor agonist, dimaprit. *Biochem. Pharmacol.* 26 2076 1977
18. Verma S.C. & McNeill J.H.. H<sub>2</sub>-histaminergic activity of clonidine in the guinea pig heart. *J Cyclic Nucleot. Res.* 3 95 1977
- 19 Wallard A. cAMP as a second messenger in central blood pressure control. *Naunyn-Schmiedeberg's Arch Pharmacol.* 290 419 1978
- 20 White A., Handler P. & Smith, E.L. *Principles of Biochemistry* McGraw-Hill New York (1973) pp. 697—699
- 21 Van Zwieten, P.A. Antihypertensive drugs with a central action. *Progr Pharmacol.* 1 1 1976

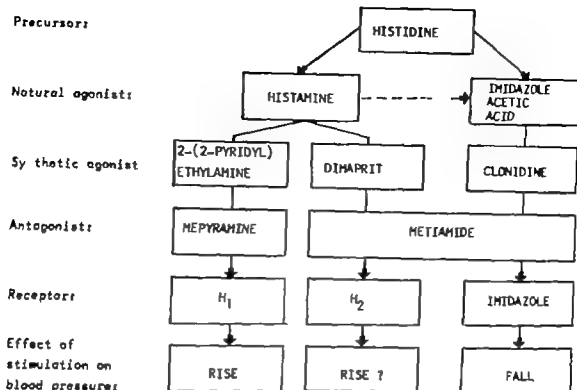


Fig. 2. Hypothesis of the role of histamine  $H_1$  and  $H_2$ -receptors, and "imidazole receptors" in the central control of blood pressure. For further explanation, see the text.

### ACKNOWLEDGEMENTS

This work was done under a contract with the Association of Finnish Life Insurance Companies. It was also partly supported by a grant from the Paavo Nurmi Foundation. The skilful technical assistance of Mrs. Sirpa Rutanen, Miss Taina Heikkinen and Miss Eila Pesonen is gratefully acknowledged. We are much obliged to Mrs. Leena Pyykkö and Mrs. Helena Saari for their efficient secretarial assistance.

### REFERENCES

1. Audigier Y., Virion A. & Schwartz J.-C. Stimulation of cerebral histamine  $H_2$  receptors by clonidine. *Nature* 262 307 1976
2. Baudry M., Marrazzi M.P. & Schwartz J.-C.  $H_1$  and  $H_2$ -receptors in the histamine induced accumulation of cyclic AMP in guinea-pig brain slices. *Nature* 253 352 1975
3. Black J.W., Duncan W.A.M., Emmett J.C., Ganellin C.R., Hesselbo T., Parsons M.E. & Wyllie J.H. Metlamide - an orally active histamine  $H_2$ -receptor antagonist. *Agents Actions* 3 133 1973
4. Brimblecombe R.W., Duncan W.A.M., Owen D.A.A. & Parsons M.E. The pharmacology of burimamide and metlamide, two histamine  $H_2$ -receptor antagonists. *Feder. Proc.* 35 1931 1976

## MATERIAL AND METHODS

Fourteen patients (9 men and 5 women) with essential hypertension took part in the study. Their mean age was 53 years (28-66 years). All patients included were initially treated for at least 3 weeks with diuretic agents only, i.e. without potassium supplements. Seven patients were treated with bendroflumethiazide 5 mg once daily, 4 patients with hydrochlorothiazide 50 mg once daily, 2 patients with chlor-thalidone 50 mg once daily, and 1 patient with mefruside 50 mg o.c. daily.

The patients were then given combination therapy by adding atenolol 100 mg daily to the previous diuretic treatment for an additional 3 week period.

Measurements of blood pressure were done indirectly using a sphygmomanometer (cuff rubber bag 13-35 cm). Recumbent heart rate and blood pressure were recorded after the patient had rested for 5 min. Diastolic blood pressure was taken at the point of disappearance of the Korotkoff sound (phase 5). Electrolyte and uric acid in serum and urine were assessed on two consecutive days. All measurements were done in the hospital before and at the end of the period of combination therapy.

Statistical analysis was made with Student's t test for paired data.

## RESULTS

Statistically significant reductions of standing and recumbent

COMBINATION THERAPY WITH SALURETICS AND ATENOLOL  
IN ESSENTIAL HYPERTENSION.

Effects on blood pressure, electrolytes and uric acid.

Thorkell Gudbrandsson and Lennart Hansson

From the Department of Medicine Östra Hospital  
University of Göteborg Göteborg Sweden

Saluretics and beta-adrenoceptor blocking agents constitute the most common types of antihypertensive therapy today. As treatment of hypertension always is of a chronic nature side effects caused by treatment are of great importance. The metabolic side effects seen during diuretic treatment namely hypokalemia and hyperuricemia are well known but their importance during chronic treatment is still a matter of some controversy (3-8).

Side effects during beta adrenoceptor blockade are to a great extent well known (5). Unwanted metabolic effects do occur but their clinical importance remains unclear. However effects on electrolytes and uric acid have been considered unimportant (3). Recent investigations indicate that combined treatment with saluretics and a beta-adrenoceptor blocking agent may be of interest in this respect (6-7).

The purpose of the present investigation which is an open pilot study was to study effects on electrolytes and uric acid during combined treatment with saluretics and the beta-1-selective adrenoceptor blocker atenolol.

## MATERIAL AND METHODS

Fourteen patients (9 men and 5 women) with essential hypertension took part in the study. Their mean age was 53 years (28-66 years). All patients included were initially treated for at least 5 weeks with diuretic agents only, i.e. with potassium supplements. Seven patients were treated with bendroflumethiazide 5 mg o.c. daily, 4 patients with hydrochlorothiazide 50 mg once daily, 2 patients with chlorothalidate 50 mg once daily, and 1 patient with mefruside 50 mg o.c. daily.

The patients were then given combination therapy by adding furosemide 100 mg daily to the previous diuretic treatment for an additional 5 week period.

Measurements of blood pressure were done indirectly using mercury sphygmomanometer (uffraber hg 13 x 35 cm). Resting heart rate and blood pressure were recorded after 5 minutes of rest. End-tidal pressure was recorded after standing for 2 minutes. Diastolic blood pressure was taken at the point of disappearance of the Korotkoff sounds (phase 5). Electrolyte and uric acid in serum and urine were measured twice each day. All measurements were done throughout the study before and at the end of the period of combination therapy.

Statistical analysis was done with Student's t-test for paired data.

## RESULTS

Statistically significant reductions of standing and supine

COMBINATION THERAPY WITH SALURETICS AND ATENOLOL  
IN ESSENTIAL HYPERTENSION.

Effects on blood pressure, electrolytes and uric acid,

Thorkell Gudbrandsson and Lennart Hansson

From the Department of Medicine Östra Hospital  
University of Göteborg Göteborg Sweden

Saluretics and beta-adrenoceptor blocking agents constitute the most common types of antihypertensive therapy today. As treatment of hypertension always is of a chronic nature side effects caused by treatment are of great importance. The metabolic side effects seen during diuretic treatment, namely hypokalemia and hyperuricemia, are well known but their importance during chronic treatment is still a matter of some controversy (3-8).

Side effects during beta-adrenoceptor blockade are to a great extent well known (5). Unwanted metabolic effects do occur but their clinical importance remains unclear. However, effects on electrolytes and uric acid have been considered unimportant (3). Recent investigations indicate that combined treatment with saluretics and a beta-adrenoceptor blocking agent may be of interest in this respect (6-7).

The purpose of the present investigation, which is an open pilot study, was to study effects on electrolytes and uric acid during combined treatment with saluretics and the beta-1-selective adrenoceptor blocker atenolol.

this effect however is not well studied and is obviously quite complex. It should be noted that diuretics usually have quite opposite effects on the renin-angiotensin system compared with beta-adrenoceptor blockers. In some patients this could be of great importance e.g. patients with a poor response to diuretic treatment because of angiotensin II depending hypertension (2). Such patients could be expected to respond favourably to combined treatment with diuretics and beta-adrenoceptor blockers.

The relatively marked increase of serum chloride found in the present investigation was unexpected and is difficult to explain. The possible clinical importance of this change is uncertain as is the tendency towards reduced calcium excretion in the urine.

Wilson and Mitchell have shown that tenolol given as the sole therapy caused a significant reduction of serum urate (7). On the other hand they observed a marked increase of serum urate after combined therapy with tenolol and bendroflumethiazide (7). With non-selective beta-adrenoceptor blocking agents a certain increase of serum urate has been reported (4) although in addition to previous diuretic therapy (5). In the present study only a minor and insignificant increase of serum urate was seen during the combined treatment. Therefore it is possible that tenolol differs from e.g. propranolol in this respect.

I cannot rule out a certain metabolic effect on rate and electrolyte balance demonstrated in the present investigation during combined therapy with tenolol and diuretics. The clinical relevance of the increase in serum potassium could be regarded as risk factor for cardiac arrhythmias. However, the clinical importance of some of the other changes remains to



blood pressure and heart rate were seen when atenolol was added to the initial saluretic regimen (Table I) As regards the biochemical parameters a small but statistically significant increase of serum potassium was obtained after the addition of atenolol Concomitantly with this urinary excretion of potassium tended to go down No changes of serum sodium occurred Serum chloride increased significantly whereas serum calcium was unchanged The reduction of calcium excretion in the urine was at the limit of statistical significance ( $p = 0.05$ ) Serum urate tended to increase whereas urinary excretion of uric acid was unchanged (For full details see Table I)

Side effects were reported by 4 patients during combined treatment (fatigue 2 impotence 1 and vertigo 1) One patient developed temporary atrial fibrillation

### DISCUSSION

It is well known that combined treatment with saluretics and beta-adrenoceptor blocking agents can normalize blood pressure in a great proportion of patients with hypertension Thus our finding of an additional antihypertensive effect when atenolol was added to the previous diuretic regimen was not unexpected

Atenolol has previously been shown to increase serum potassium (7) In the present study we have demonstrated this effect also during combined treatment with diuretics This effect is possibly due to the renin suppressive action which has been demonstrated for atenolol (1) The exact nature of

# REFERENCES

- 1 Aberg H : Plasma renin activity after the use of beta adrenergic blocking agent Int J Clin Pharmacol 9: 98 1974
- 2 Anderson G H Dalakas I M Elias A Tomycz H & Street D H P Diuretic therapy and response of essential hypertension to Spironolactone Int Med 87: 183 1977
- 3 Bengtsson C Snerdt R & Werkö L : Saluretic in diuretic hypertension and handling Läkertidn 71: 2997 1974
- 4 Berglund G & Anderson U : The doses of hydrochlorothiazide in hypertension Antihypertensive and metabolic effects Europ J Clin Pharmacol 10: 177 1976
- 5 Hansen L & Werkö L : Handling of hypertension medication with respect to electrolyte balance Läkertidn 72 959 1975
- 6 Hjeltnes A Hjerpe I Lerer P & Holme I : Possible metabolic side effect of beta adrenergic blocking drug Brit med J 1: 828 1978
- 7 Wilco R G & Mitchell J R A : Combination of atenolol bendroflumide and hydrochlorothiazide in the treatment of severe hypertension Brit med J 2 547 1977
- 8 Wilkin P R Insel M H Hap M & Hefery E B : Total body and renal potassium during prolonged thiazide therapy for essential hypertension Lancet 1: 759 1975

Table I Effect on Blood Pressure (mm Hg) Heart Rate (beats/min) and Biochemical Variables (mean  $\pm$  S E M)

				Saluretics		Difference	p <
				Saluretics	Atenolol		
Recumb	Syst	BP	(n 14)	169 ± 5.1	148 ± 5.2	-21 ± 4.8	0.001
Recumb	Diast	BP	(n 14)	100 ± 3.3	86 ± 2.3	-14 ± 3.3	0.001
Erect	Syst	BP	(n=14)	161 ± 5.5	135 ± 6.0	-26 ± 4.3	0.001
Erect	Diast	BP	(n=12)	102 ± 3.8	88 ± 3.2	-14 ± 3.4	0.002
Heart Rate			(n=14)	77 ± 4.1	63 ± 3.7	-14 ± 3.8	0.01
S-Potassium	mmol/l		(n=12)	3.8 ± 0.09	3.9 ± 0.09	0.14 ± 0.06	0.05
S-Sodium	mmol/l		(n 12)	139 ± 0.7	140 ± 0.7	1.0 ± 0.7	ns
S-Chloride	mmol/l		(n 12)	98 ± 1.1	102 ± 1.5	4 ± 1.1	0.01
S-Calcium	mmol/l		(n 12)	2.35 ± 0.03	2.33 ± 0.03	-0.02 ± 0.03	ns
S-Urate	μmol/l		(n 12)	314 ± 21	335 ± 29	21 ± 18	ns
U-Potassium	mmol/24h		(n 13)	76 ± 7	65 ± 6	-11 ± 9	ns
U-Calcium	mmol/24h		(n 11)	5.0 ± 0.6	3.9 ± 0.4	-1.1 ± 0.5	0.05
U-Urate	mmol/24h		(n=11)	3.1 ± 0.2	3.0 ± 0.3	-0.1 ± 0.4	ns

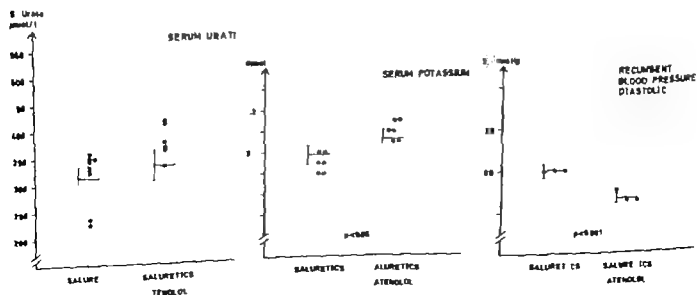


Figure 1

Some effects of combined therapy with saluretic

and atenolol

artery using the Seldinger technique. Continuous intra arterial measurement is then performed using a strain gauge transducer AE 840 (Aker Horten Norway) placed at the middle of the fore arm connected to an electro manometer (Simonsen & Weel Copenhagen, Denmark). Continuous flushing of the system with Heparin saline is performed using an "Intraflow" unit (Anderson USA). The manometer is connected to a digital display unit from which systolic and diastolic BP can be read from pulse beat to pulse beat. The manometer is further connected to a Memory Trendscope MTS 216 (Simonsen & Weel Copenhagen Denmark) where the intra arterial curve can be observed during the whole study. The memory function of the oscilloscope has 120 points for systolic and 120 points for diastolic pressures. The memory can be chosen to registrate blood pressure every 15 sec during 1 hour every 30 sec during 1 hour or every 120 sec during 4 hours. In this study mainly the two last registrations were used. Every hour or every third hour during the 24 hour registration the memory has to be emptied. This is done very quickly (about 20 seconds). The recorded pressures are registered on a writing unit (Mingograph Elma Siemens Sweden). When all 24 hours registration has been performed the whole intra arterial curve can be constructed and average blood pressure for every hour can be calculated using "optical intergration". From this curve mean daytime and mean nighttime BP (06 a.m.) can be calculated. Three to four times during the day repeated auscultatory and intra arterial comparisons is performed in every subject using direct registration of intra arterial BP and indirect measurements of right arm BP in order to establish the accuracy of auscultatory BP in the single patient. The catheter is withdrawn on the morning at day 3 and meticulous compression of the puncture site is established in order to avoid any bleeding from the brachial artery. The patient left the hospital at day 3 for new repeated control visits at out patient clinic.

## RESULTS

The auscultatory BP decreased in nearly all subjects during hospital stay (Table I, Fig. 1). The average decrease in systolic BP was 15 mm Hg and in diastolic BP 11 mm Hg. In three of the subjects the decrease in diastolic BP was more than 20 mm Hg. The average intra arterial diastolic BP at daytime was in one of the borderline hypertensive subjects and 6 of the treated hypertensive subjects more than 20 mm Hg lower than diastolic BP at out patient clinic. The mean difference of all subjects being 14 mm Hg for systolic BP and 11 mm Hg for diastolic BP. The accuracy of auscultatory arm BP registration is given in Fig. 1 (Third column for left). In the single patient the difference auscultatory intra arterial BP varied few mm Hg from time to time. As a whole auscultatory systolic BP was 4 mm Hg lower than intra arterial systolic BP, while auscultatory diastolic BP was 6 mm Hg higher. In one of the 12 patients there was a substantial difference in diastolic pressure of about 20 mm Hg. In this patient BP at out patient clinic was in average 190/123 mm Hg, auscultatory BP at hospital 179/104 mm Hg, corresponding intra arterial BP 170/85 mm Hg, while mean daytime BP was about 180/90 mm Hg.

With the present equipment it is possible to follow the intra arte

# INTRA-ARTERIAL BLOOD PRESSURE MEASURED DURING 24-HOURS IN EVALUATION OF HYPERTENSIVE SUBJECTS

POUL EBBE NIELSEN & TAGE HILDEN

MEDICAL DEPT C DIAKONISSESTIFTELSEN DK-2000 COPENHAGEN F DENMARK

Diagnosis of hypertension and the effect of antihypertensive treatment is based on measurements of auscultatory arm blood pressure (BP) during repeated visits to out-patient clinic i e repeated casual blood pressures. In these indirect measurements two main problems are included: 1 discrepancy between auscultatory BP and intra-arterial BP, 2 discrepancy between casual BP measured at out-patient clinic and mean BP of the unobserved patient during daily life activities. When several studies have been published concerning the accuracy of auscultatory BP tested against intra-arterial measurements (conf. 4) only few investigations have dealt with the fundamental problem of casual BP tested against daily life BP in hypertensive subjects. Using semiautomathical equipment for repeated indirect measurements of arm BP, Irwing & al. (1) as well as Sokolow & al. (6) demonstrated that casual BP tended to be much higher than the mean BP measured repeatedly during daytime, while Lund-Johansen (3) demonstrated good agreement between casual BP and mean daytime BP. Using continuously intra-arterial registration of BP during daily life activities, Littler & al. (2) demonstrated in few patients with hypertension WHO-group I that casual BP was significantly higher than mean daytime BP, while good agreement was found in a group of treated hypertensive subjects. In our study we have compared casual BP to intra-arterial BP measured during 24-hours on hospital in a group of borderline hypertensive subjects as well as a group of badly controlled hypertensive patients. Furthermore we performed in each subject repeated comparisons between auscultatory and intra-arterial blood pressures.

## MATERIAL AND METHOD

The patients studied were (Table I): 1 Four untreated borderline hypertensive males aged 25 to 51 years with diastolic BP (Phase V) at out-patient clinic between 95 and 108 mm Hg, 2 Twelve treated hypertensive subjects with essential hypertension (8 males, 4 females) aged 42 to 68 years with DBP  $\geq$  105 mm Hg during repeated measurements at out-patient clinic. The antihypertensive therapy was different from patient to patient but it was characteristic to all the patients in this group that the blood pressure was insufficiently controlled on antihypertensive therapy which often was given as combined therapy. During the whole study the antihypertensive therapy was unchanged. All the subjects are followed at out-patient clinic in several visits before and after the intra-arterial measurement in order to get a stable baseline for auscultatory BP. Then the subjects are hospitalized for 3 days. In the morning at day 2 the patient is placed comfortable in the bed and a 1.0 mm polyethylene catheter (Surgimed Ølstykke, Denmark) is inserted in the left brachial

artery using the Seldinger technique. Continuous intra arterial measurement is then performed using a strain gauge transducer AE 840 (Aker, Horten Norway) placed at the middle of the forearm connected to an electro manometer (Simonsen & Weel Copenhagen, Denmark). Continuous flushing of the system with Heparin saline is performed using an "Intraflow" unit (Anderson USA). The manometer is connected to a digital display unit from which systolic and diastolic BP can be read from pulse beat to pulse beat. The manometer is further connected to a Memory Trendscope MTS 216 (Simonsen & Weel Copenhagen Denmark) where the intra arterial curve can be observed during the whole study. The memory function of the oscilloscope has 120 points for systolic and 120 points for diastolic pressures. The memory can be chosen to registrate blood pressure every 15 sec during 1 hour every 30 sec during 1 hour or every 120 sec during 4 hours. In this study mainly the two last registrations were used. Every hour or every third hour during the 24 hour registration the memory has to be emptied. This is done very quickly (about 20 seconds). The recorded pressures are registered on a writing unit (Mingograph Elma Simonsen Sweden). When all 24 hours registration has been performed the whole intra arterial curve can be constructed and average blood pressure for every hour can be calculated using "optical intergration". From this curve mean daytime and mean nighttime BP (06 a.m.) can be calculated. Three to four times during the day repeated auscultatory and intra arterial comparisons is performed in every subject using direct registration of intra arterial BP and indirect measurements of right arm BP in order to establish the accuracy of auscultatory BP in the single patient. The catheter is withdrawn on the morning at day 3 and meticulous compression of the puncture site is established in order to avoid any bleeding from the brachial artery. The patient left the hospital at day 3 for new repeated control visits at out patient clinic.

## RESULTS

The auscultatory BP decreased in nearly all subjects during hospital stay (Table 1, Fig. 1). The average decrease in systolic BP was 15 mm Hg and in diastolic BP 11 mm Hg. In three of the subjects the decrease in diastolic BP was more than 20 mm Hg. The average intra arterial diastolic BP at daytime was in one of the borderline hypertensive subjects and 6 of the treated hypertensive subjects more than 20 mm Hg lower than diastolic BP at out patient clinic the mean difference of all subjects being +14 mm Hg for systolic BP and 18 mm Hg for diastolic BP. The accuracy of auscultatory arm BP registration is given in Fig. 1 (Third column for left). In the single patient the difference auscultatory intra arterial BP varied few mm Hg from time to time. As a whole auscultatory systolic BP was 4 mm Hg lower than intra arterial systolic BP while auscultatory diastolic BP was 6 mm Hg higher. In one of the 12 patients there was a substantial difference in diastolic pressure of about 20 mm Hg. In this patient BP at out patient clinic was in average 190/123 mm Hg, auscultatory BP at hospital 179/104 mm Hg corresponding intra arterial BP 170/85 mm Hg, while mean daytime BP was about 180/90 mm Hg.

With the present equipment it is possible to follow the intra arte

## INTRA-ARTERIAL BLOOD PRESSURE MEASURED DURING 24-HOURS IN EVALUATION OF HYPERTENSIVE SUBJECTS.

POUL EBBE NIELSEN & TAGE HILDEN  
MEDICAL DEPT C DIAKONISSESTIFTELSEN DK-2000 COPENHAGEN F  
DENMARK

Diagnosis of hypertension and the effect of antihypertensive treatment is based on measurements of auscultatory arm blood pressure (BP) during repeated visits to out-patient clinic 1 e repeated casual blood pressures In these indirect measurements two main problems are included 1 discrepancy between auscultatory BP and intra-arterial BP 2 discrepancy between casual BP measured at out-patient clinic and mean BP of the unobserved patient during daily life activities When several studies has been published concerning the accuracy of auscultatory BP tested against intra-arterial measurements (conf 4) only few investigations have delt with the fundamental problem of casual BP tested against daily life BP in hypertensive subjects Using semiautomathical equipment for repeated indirect measurements of arm BP Irving & al (1) as well as Sokolow & al (6) demonstrated that casual BP tended to be much higher than the mean BP measured repeatedly during daytime while Lund-Johansen (3) demonstrated good agreement between casual BP and mean daytime BP Using continuously intra-arterial registration of BP during daily life activities Littler & al (2) demonstrated in few patients with hypertension WHO-group I that casual BP was significantly higher than mean daytime BP while good agreement was found in a group of treated hypertensive subjects In our study we have compared casual BP to intra-arterial BP measured during 24-hours on hospital in a group of borderline hypertensive subjects as well as a group of badly controlled hypertensive patients Furthermore we performed in each subject repeated comparisons between auscultatory and intra-arterial blood pressures

### MATERIAL AND METHOD

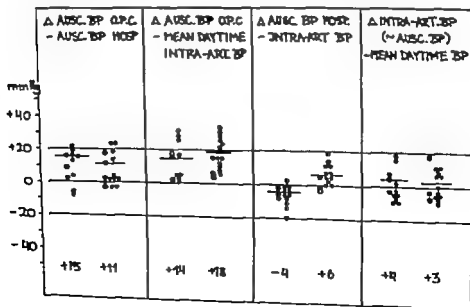
The patients studied were (Table I) 1 Four untreated borderline hypertensive males aged 25 to 51 years with diastolic BP (Phase V) at out-patient clinic between 95 and 108 mm Hg 2 Twelve treated hypertensive subjects with essential hypertension (8 males 4 females) aged 42 to 68 years with DBP  $\geq$  105 mm Hg during repeated measurements at out-patient clinic The antihypertensive therapy was different from patient to patient but it was characteristic to all the patients in this group that the blood pressure was in sufficiently controlled on antihypertensive therapy which often was given as combined therapy During the whole study the antihypertensive therapy was unchanged All the subjects are followed at out-patient clinic in several visits before and after the intra-arterial measurement in order to get a stable baseline for auscultatory BP Then the subjects are hospitalized for 3 days In the morning at day 2 the patient is placed comfortable in the bed and a 1.0 mm polyethylene catheter (Surgimed Ølstykke Denmark) is inserted in the left brachial

**TABLE 1**  
Blood Pressure (mm Hg) measured by Auscultation at Out Patient Clinic (O P C) compared to Intra arterial Blood Pressure measured during 24 hours at Hospital

		BP at O P C		BP at Hospital			
		before and after Admittance to Hospital		BP compared to Itra rt BP		Itra rt BP	
		Before	After	Ausc BP	Itra rt BP	Average BP at daytime	Average BP at night
Borderline	mean	159/99	152/98	146/91	153/89	145/85	119/73
Hypertensive	range	152/88	155/92	128/85	156/83	158/80	110/68
n = 4		170/108	165/106	168/97	169/98	150/90	130/80
Treated Hypertensive							(n = 7)
DBP > 105 mmHg	mean	192/118	180/111	179/108	184/102	183/89	163/82
12	range	170/105	160/95	132/78	145/81	140/70	130/80
		230/138	223/137	217/132	226/128	220/122	215/110

**FIG 1**

Individual difference of systolic and diastolic blood pressure (left respectively right columns) recorded in 4 borderline hypertensive subjects (open circles) and 12 treated hypertensive subjects. Further information see the text O P C = out patient clinic





rial BP during unobserved as well as observed state ex when nurses or doctors are coming into the room in order to measure the auscultatory BP

In the main group of investigated subjects there was almost no difference between intra-arterial BP when the patients was observed compared to unobserved condition (Fig 1 right column)

However in two of the patients it was evident that the simple procedure of auscultatory measurement was sufficient to give a rise in intra-arterial BP (Fig 1)

In a 51-year old man with borderline hypertension auscultatory BP at out-patient clinic was in average 170/95 mm Hg auscultatory BP at hospital 168/97 mm Hg corresponding intra-arterial BP 169/98 mm Hg while mean daytime BP was 145/80 mm Hg The other patient was a 52-year old female auscultatory BP at out-patient clinic 230/135 mm Hg at hospital 217/121 mm Hg corresponding intra-arterial BP 218/114 mm Hg while mean daytime BP was about 190/100 mm Hg BP during night was in the borderline hypertensive in average 119/73 mm Hg - in several hours during sleep even much lower Among treated hypertensive subjects a decrease was also found (Table I) but only among the patients where sleep was observed

## DISCUSSION

In this study we have compared measurements at out-patient clinic to measurements during hospitalization with all subjects in supine position during the 24 hours It might there fore be argued that our measurements are not comparable to earlier investigations where the patients are tested during daily life activities This might explain our big difference between BP at out-patient clinic and mean daytime intra-arterial BP We have mainly used the present measurements to test the single patient on two points a accuracy of auscultatory BP against intra-arterial BP b BP during unobserved conditions compared to observed conditions If no substantial difference is found in the single patient we feel it is justified to increase the antihypertensive therapy in order to get the casual BP sufficiently controlled Contrary if big differences exists these differences should be taken into account when therapy is discussed As mentioned we demonstrated in one subject a big inaccuracy of auscultatory BP compared to intra-arterial BP and in two subjects a big difference between intra-arterial BP during unobserved and observed condition No severe complications to the intra-arterial procedure were observed We have tried to correlate our findings to hypertensive organ damages but in this small group of subjects we were unable to find any correlation to organ damages

At last a citation from G Pickering (5)

'What we can say then is that the arterial pressure as measured in the clinic is a useful measurement so long as the doctor does not depend too slavishly upon it or give it greater significance in assessing the patients condition than it deserves

## ACKNOWLEDGEMENT

The study was supported by grants from Carlsberg Mindelegat and Det Lægevidenskabelige Fond for Stor-København Grønland og Færøerne

# RENIN ANGIOTENSIN SYSTEM AND SYMPATHETIC NERVE ACTIVITY IN MILD ESSENTIAL HYPERTENSION. THE FUNCTIONAL SIGNIFICANCE OF ANGIOTENSIN II IN UNTREATED AND THIAZIDE TREATED HYPERTENSIVE PATIENTS.

H. ISEN A LETH H HOLLNAGEL A M KAPPELGAARD M. DAMKJER  
NIELSEN M J CHRISTENSEN J GIERE DEPT OF CLINICAL PHYSIO-  
LOGY AND MEDICAL DEPT B GLOSTRUP HOSPITAL COPENHAGEN MEDI-  
CAL DEPT F HERLEV HOSPITAL AND SECOND CLINIC OF INTERNAL  
MEDICINE ÅRHUS KOMMUNEHOSPITAL DENMARK

## INTRODUCTION

Measurement of plasma renin activity on blood sample from patient with essential hypertension and normotensive controls have led to classification of patients with essential hypertension into renin-subgroup (1,2). This approach has not settled the role of angiotensin II in the maintenance of hypertension. By means of specific competitive inhibitor of angiotensin II e.g. saralasin it is now possible to assess the participation of angiotensin II in hypertension in a more direct way.

The role of the sympathetic nervous system has also been a subject of continuing debate. Whereas some investigators have found increased plasma catecholamine concentration in essential hypertension this has been refuted by others (3).

The aim of the present study has been to investigate by means of saralasin the functional significance of the renin-angiotensin system (RAS) in the maintenance of high blood pressure in a homogenous group of patients with mild essential hypertension and measure plasma norepinephrine concentration in the same group of patients.

## PATIENTS AND METHODS

25 patients (7 F, 18 M) with essential hypertension (WHO I) identified during a survey of a population born in 1936 were investigated. None of the patients had ever received antihypertensive treatment. 25 healthy, age-old normotensive individuals (1 F, 15 M) selected from the same population served as a control group. Plasma renin concentration (PRC), plasma angiotensin II concentration (PA II), plasma aldosterone concentration (PAC) and plasma norepinephrine concentration were measured in the sodium replet state: supine at rest and after intravenous administration of furosemide with subsequent quiet ambulation. Plasma volume (PV) and exchangeable sodium ( $Na_E$ ) were also determined in the sodium replet state.

## REFERENCES

- 1 Irwing & al Brit Heart J 1974, 36 859-866
- 2 Littler & al Circulation 1975 51 1101-1106
- 3 Lund-Johansen P T norske Lægeforen 1971 91 1509-1514
- 4 Nielsen P E & Janniche H Acta Med Scand 1974 195  
403-409
- 5 Pickering G Am J Med 1972 52 570-583
- 6 Sokolow, M & al Circulation 1966 34 279-297

Treatment with hydrochlorothiazide revealed that the group of hypertensive could be divided into 11 thiazide-responders and 10 thiazide-nonresponders with a fall in diastolic blood pressure of 10 mm Hg or more during treatment as the criterion. In the group of responders systolic blood pressure changed from 151 mm Hg (131-184) to 134 (120-145) and diastolic blood pressure decreased from 106 (98-113) to 92 (84-98) while in the 10 non-responders systolic and diastolic blood pressure was 147 mm Hg (131-184) and 103 mm Hg (95-111) respectively before treatment only changing insignificantly on thiazide.

During treatment PV decreased significantly 3-4% on average the decrease being similar in thiazide-responders and non-responders.  $Na_E$  did not change significantly. Although the natriuretic effect is of importance for the antihypertensive action of thiazide this could not explain the antihypertensive response since change in PV and  $Na_E$  were similar in thiazide-responders and non-responders.

The determining factor for the quantitative blood pressure response to thiazide treatment proved to be the responsiveness of the renin-angiotensin system. This conclusion is supported by the much higher PRC and PA II values in thiazide non-responders as compared to thiazide-responders. During treatment PRC was 96 mIU/l (71-262) in the group of non-responders and 49 mIU/l (35-142) in responders ( $p < 0.02$ ). Similarly PA II was 37 pmol/l (23-61) and 26 pmol/l (14-41) ( $p < 0.05$ ). PAC did not differ in the two groups. The importance of the RAS emerges even more convincing from the outcome of the enalapril infusions in the thiazide-treated patients showing that all thiazide-nonresponders exhibited a 10% or more decrease in MAP while only 4 out of 11 thiazide-responders showed a borderline decrease. There was a close inverse relation between change in MAP during enalapril infusion and pre-infusion level of PA II ( $r = -0.70$ ,  $p < 0.01$ ) the fall in MAP being more pronounced when pre-infusion PA II was high. Furthermore whereas supine resting PRC and PA II values before treatment did not differ in the two groups of patients pre-treatment furosemide-stimulated PRC and PA II were higher in the group of thiazide-nonresponders as compared to thiazide-responders. PRC being 84 mIU/l (42-162) and 41 mIU/l (14-106) in non-responders and responders respectively ( $p < 0.05$ ). Similarly PA II was 37 pmol/l (12-72) and 14 pmol/l (6-32) ( $p < 0.05$ ). PAC did not differ in the two groups of patients.

( $0.54 - 5.4$  nmol/kg/min) was carried out in supine position in the sodium replete state. Blood pressure (arteriosonde 1217) was recorded at 2 min intervals during a 30 min control period during 35 min of saralasin infusion and during 30 min after cessation of infusion.

21 patients were treated with hydrochlorothiazide, mean dose 75 mg/day for 3 months and the examinations were repeated. Figures are presented as median values with range in brackets.

### RESULTS AND DISCUSSION

In the group of hypertensive patients PRC, PA, II and PAC supine at rest did not differ from reference values in the 40 year old normotensive subjects. Values after acute stimulation were also nearly identical. Thus within this frame of reference a clear-cut division of the present homogenous group of patients with mild essential hypertension into renin subgroups did not emerge. In accordance with the proposal that low renin hypertension reflects a stage in the development of essential hypertension and not a distinct entity (3) a classification into renin- or angiotensin-subgroups may well tend to disappear when age, duration and severity of hypertension are identical.

Normal values of PRC and PA, II per se do not exclude the implication of RAS in the maintenance of hypertension. However, in the untreated sodium replete state angiotensin II blockade by means of saralasin only caused a significant decrease in mean arterial pressure (MAP) in two out of twenty-five patients and in the group as a whole MAP actually increased from 108 mm Hg to 111 mm Hg ( $p < 0.05$ ). Similarly, an agonistic effect of saralasin on adrenal receptors was discovered as PAC increased by 120% across saralasin infusion ( $p < 0.01$ ). Apparently, in mild essential hypertension angiotensin II has no decisive role in the maintenance of high blood pressure.

Based upon a positive correlation between age and plasma catecholamine concentration, some investigators have claimed that elevated plasma catecholamine levels in patients with essential hypertension could be explained by age differences between the hypertensive patients and the normotensive controls (4). However, this point

Treatment with hydrochlorothiazide revealed that the group of hypertensive could be divided into thiazide-responders and thiazide nonresponders with a fall in diastolic blood pressure of 1 mm Hg or more during treatment as the criterion. In the group of responders systolic blood pressure changed from 151 mm Hg (131-184) to 134 (120-145) and diastolic blood pressure decreased from 106 (98-113) to 92 (84-98) while in the 10 nonresponders systolic and diastolic blood pressure was 147 mm Hg (131-184) and 103 mm Hg (95-111) respectively before treatment only changing insignificantly on thiazide.

During treatment PV decreased insignificantly 3-4% on average the decrease being similar in thiazide-responders and nonresponders.  $\text{Na}_2\text{E}$  did not change insignificantly. Although the natriuretic effect is of importance for the antihypertensive action of thiazides this could not explain the antihypertensive response since change in PV and  $\text{Na}_2\text{E}$  were similar in thiazide-responders and nonresponders.

The different factors for the quantitative blood pressure response to thiazide treatment proved to be the responsiveness of the renin-angiotensin system. This conclusion is supported by the much higher PRC and PA II values in thiazide nonresponders as compared to thiazide-responders. During treatment PRC was 96 mIU/l (71-262) in the group of nonresponders and 49 mIU/l (35-142) in responders ( $p < 0.02$ ). Similarly PA II was 37 pmol/l (23-61) and 26 pmol/l (14-41) ( $p < 0.05$ ). PAC did not differ in the two groups. The importance of the RAS emerges even more convincing from the outcome of the enalapril infusions in the thiazide-treated patients showing that all thiazide nonresponders exhibited a clear cut decrease in MAP while only 4 out of 11 thiazide responders showed a borderline decrease. There was a close inverse relation between change in MAP during enalapril infusion and pre-infusion level of PA II ( $r = -0.70$ ,  $p < 0.001$ ) the fall in MAP being more pronounced when pre-infusion PA II was high. Furthermore whereas supine resting PRC and PA II values before treatment did not differ in the two groups of patients pre-treatment furosemide-stimulated PRC and PA II were higher in the group of thiazide nonresponders as compared to thiazide-responders PRC being 84 mIU/l (42-162) and 41 mIU/l (14-106) in nonresponders and responders respectively ( $p < 0.05$ ). Similarly PA II was 37 pmol/l (12-72) and 14 pmol/l (6-32) ( $p < 0.05$ ). PAC did not differ in the two groups of patients.

Although the patients could not be classified into low-normal-high renin subgroups, it is pertinent that they showed hypo-normo- and hyperresponsiveness of the renin-angiotensin system. Thus acutely stimulated PRC and PA II could to some extent predict the subsequent response to chronic thiazide treatment. Several counter-regulatory mechanisms might be operative during thiazide treatment, e.g. the sympathetic nervous system. During treatment plasma noradrenaline concentration increased slightly to a similar degree in both "thiazide-nonresponders" and "thiazide responders". Consequently differences in sympathetic nerve activity, as defined from measurements of plasma noradrenaline concentration, did not explain differences in the blood pressure response to thiazide treatment.

#### CONCLUSION:

In mild untreated essential hypertension angiotensin II has no decisive role in the maintenance of high blood pressure. The functional significance of RAS emerges after thiazide treatment. Thiazide-induced stimulation of RAS counterbalances the hypotensive effect of thiazide in some 40% of the treated patients. Thus the responsiveness of RAS determined the quantitative blood pressure response to treatment. Pre-treatment furosemide-stimulated PRC and PA II to some extent predicted the subsequent response to thiazide treatment.

#### ACKNOWLEDGMENT

We would like to thank Dr Michael C L Cox, Eaton Laboratories, Norwich, New York, for generous supplies of saralasin.

TABLE 1

Plasma renin concentration (PRC) angiotensin II concentration (PA II) aldosterone concentration (PAC) and norepinephrine concentration (PNC) at rest supine and after furosemide + ambulation (Median value and range in bracket)

		Essential hypertension		Normotensive controls
		n = 25		n = 25
PRC(mIU/l)	Rest	29(11-67)	n.s.	31(11-49)
	Furo + Amb	57(14-162)	n.s.	78(17-225)
PAII(pg/ml)	Rest	8(4-22)	n	10(4-20)
	Furo + Amb	26(6-72)	p<0.05	35(12-91)
PAC(pmol/l)	Rest	195(56-417)	n	167(111-361)
	Furo + Amb	556(56-1446)	n.s.	667(222-2029)
PNC(nmol/l)	Rest	1.27(0.51-2.04)	n.s.	1.21(0.64-2.29)
	Furo + Amb	2.36(0.96-3.50)	n.s.	2.36(1.46-4.01)

BLOOD PRESSURE RESPONSE TO SARALASIN IN PATIENTS WITH ESSENTIAL HYPERTENSION

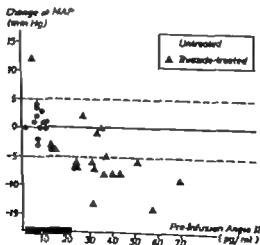


Fig. 1

Change in MAP on saralasin infusion in relation to pre-infusion plasma angiotensin II concentration (pg/ml ~ pmol/l) in patients with essential hypertension



Although the patients could not be classified into low-normal-high renin subgroups it is pertinent that they showed hypo-normo- and hyperresponsiveness of the renin-angiotensin system. Thus acutely stimulated PRC and PA II could to some extent predict the subsequent response to chronic thiazide treatment. Several counter-regulatory mechanisms might be operative during thiazide treatment e.g. the sympathetic nervous system. During treatment plasma noradrenaline concentration increased slightly to a similar degree in both "thiazide-nonresponders and thiazide responders". Consequently differences in sympathetic nerve activity, as defined from measurements of plasma noradrenaline concentration, did not explain differences in the blood pressure response to thiazide treatment.

#### CONCLUSION:

In mild untreated essential hypertension angiotensin II has no decisive role in the maintenance of high blood pressure. The functional significance of RAS emerges after thiazide treatment. Thiazide-induced stimulation of RAS counterbalances the hypotensive effect of thiazide in some 40% of the treated patients. Thus the responsiveness of RAS determined the quantitative blood pressure response to treatment. Pre-treatment furosemide-stimulated PRC and PA II to some extent predicted the subsequent response to thiazide treatment.

#### ACKNOWLEDGMENT

We would like to thank Dr Michael C L Cox, Eaton Laboratories, Norwich, New York, for generous supplies of saralasin.

# EFFECT OF SODIUM LOADING ON THE RENIN-ALDOSTERONE SYSTEM IN ESSENTIAL HYPERTENSION

E B Pedersen & H J Kornerup

Department of Medicine C Aarhus Kommunehospital and Aarhus  
University Aarhus C Denmark

## Introduction

In essential hypertension a sodium load is excreted more abruptly than in normotensive subjects. Some studies have shown an abnormal sustained aldosterone secretion during salt loading in essential hypertension. The purpose of the present investigation has been to study the relationship between the renin-aldosterone system and the urinary sodium excretion during sodium loading in young patients with mild essential hypertension and normotensive control subjects.

## Material and methods

Fifteen patients: 11 male and four female mean age 28 years (range 21-36) with mild essential hypertension (mean blood pressure =  $121 \pm 3$  (SEM) mm Hg) were studied. All drugs were discontinued for at least 6 weeks before the studies were performed. Ten healthy normotensive control subjects: five male and five female mean age 29 years (range 22-44) (mean blood pressure =  $92 \pm 2$  (SEM) mm Hg) were studied.

Blood samples for determination of plasma renin concentration (PRC) and plasma aldosterone concentration (PAC) were drawn in the morning after the end of a 40 min control period and after the intravenous infusion of 500 ml of sodium chloride solution (50 g/l) given over 40 min. Urine was collected for the determination of sodium in the control period and the infusion period.

PRC was determined by the method described by Giese et al (1) and PAC by Nielsen's method (3). Blood pressure was measured by

# REFERENCES:

- 1 Brunner, H R    Sealey J E    & Laragh J H : Renin subgroups in essential hypertension: further analysis of their pathophysiological and epidemiological characteristics  
Circulation Res 32 suppl 1: 99 1973
- 2 Gavras H    Ribeiro A H    Gavras I    & Brunner H R : Reciprocal relation between renin dependency and sodium dependency in essential hypertension    N Engl J Med 293: 1278 1976
- 3 Padfield P L    Brown J J    Lever A F    Schalekamp M A D    Beevers D G    Davies H L    Robertson J I S    & Tree M : Is low-renin hypertension a stage in the development of essential hypertension or a diagnostic entity? Lancet I: 548 1975
- 4 Pedersen E E    & Christensen N J : Catecholamines in plasma and urine in patients with essential hypertension determined by double-isotope derivative techniques    Acta med scand 198: 373 1975

E B Pedersen & H J Kornerup

Department of Medicine C Aarhus Kommunehospital and Aarhus University Aarhus C Denmark

### Introduction

In essential hypertension a sodium load is excreted more abruptly than in normotensive subjects. Some studies have shown an abnormal sustained aldosterone secretion during salt loading in essential hypertension. The purpose of the present investigation has been to study the relationship between the renin-aldosterone system and the urinary sodium excretion during sodium loading in young patients with mild essential hypertension and normotensive control subjects.

### Material and methods

Fifteen patients 11 male and four female mean age 28 years (range 21-36) with mild essential hypertension (mean blood pressure =  $121 \pm 3$  (SEM) mm Hg) were studied. All drugs were discontinued for at least 6 weeks before the studies were performed. Ten healthy normotensive control subjects five male and five female mean age 29 years (range 22-44) (mean blood pressure =  $92 \pm 2$  (SEM) mm Hg) were studied.

Blood samples for determination of plasma renin concentration (PRC) and plasma aldosterone concentration (PAC) were drawn in the morning after the end of a 40 min control period and after the intravenous infusion of 500 ml of sodium chloride solution (50 g/l) given over 40 min. Urine was collected for the determination of sodium in the control period and the infusion period.

PRC was determined by the method described by Giese et al (1) and PAC by Nielsen's method (2). Blood pressure was measured by

sphygmomanometer technique Non-parametric tests were used for the statistical analysis

### Results

Changes in PRC and PAC during sodium loading are shown in fig 1

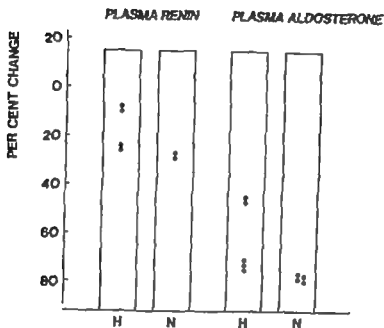


Fig 1 Changes in PRC and PAC during sodium loading in patients with essential hypertension (H) and normotensive control subjects (N)

In the hypertensive group the mean PRC fell significantly from 43 uGU/ml to 29 uGU/ml ( $p < 0.01$ ) and the mean PAC from 16.5 ng/100 ml to 5.7 ng/100 ml ( $p < 0.01$ ) during sodium loading. In the normotensive group the mean PRC fell from 34 uGU/ml to 24 uGU/ml ( $p < 0.01$ ) and the mean PAC from 13.8 ng/100 ml to 5.8 ng/100 ml ( $p < 0.01$ ). The fall in PRC and PAC in the hypertensive group did not differ significantly from the fall in the normotensive group.

The percentual increase in mean blood pressure was the same in the hypertensive (5%) and the normotensive group (4%)

The increase in urinary sodium excretion in the hypertensive group (9.75 mmol/40 min) was significantly higher ( $p < 0.05$ ) during saline infusion than in the normotensive group (5.12 mmol/40 min)

PRC and PAC were significantly correlated in both the hypertensive ( $\rho = 0.72$   $p < 0.01$ ) and the normotensive group ( $\rho = 0.80$   $p < 0.01$ ) before but not after sodium loading

The rise in urinary sodium excretion during sodium loading in the hypertensive patients was significantly correlated with the suppression of PAC ( $\rho = -0.59$   $p < 0.05$ ) but not with the fall in PRC. Changes in urinary sodium excretion in the normotensive subjects were not correlated with changes in PAC or PRC

#### Discussion and conclusion

The results indicate that the suppressibility of the renin-aldosterone system by hyperosmotic saline is normal in young patients with mild essential hypertension. The disagreement with other studies which showed an abnormal aldosterone secretion pattern during sodium loading could be attributed to differences in the amount of sodium given, the manner and duration of loading and to the fact that many patients studied previously were older and suffered from more pronounced hypertensive vascular disease (2). The rise in urinary sodium excretion with decreasing PAC suggests that PAC might be a regulatory factor in exaggerated natriuresis in young patients with mild essential hypertension.

#### References

1. Gies J, Jørgensen M, Nielsen H D, Lund J H & Munck O, Plasma renin concentration measured by use of radioimmunoassay for angiotensin I. Scand J clin Lab Invest 26:355 1970

sphygmomanometer technique Non-parametric tests were used for the statistical analysis

## Results

Changes in PRC and PAC during sodium loading are shown in fig 1

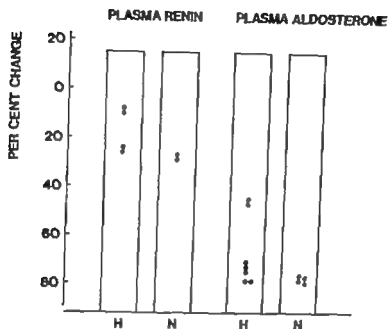


Fig 1 Changes in PRC and PAC during sodium loading in patients with essential hypertension (H) and normotensive control subjects (N)

In the hypertensive group the mean PRC fell significantly from 43 uGU/ml to 29 uGU/ml ( $p < 0.01$ ) and the mean PAC from 16.5 ng/100 ml to 5.7 ng/100 ml ( $p < 0.01$ ) during sodium loading. In the normotensive group the mean PRC fell from 34 uGU/ml to 24 uGU/ml ( $p < 0.01$ ) and the mean PAC from 13.8 ng/100 ml to 5.8 ng/100 ml ( $p < 0.01$ ). The fall in PRC and PAC in the hypertensive group did not differ significantly from the fall in the normotensive group.

The percentual increase in mean blood pressure was the same in the hypertensive (5%) and the normotensive group (4%)

The increase in urinary sodium excretion in the hypertensive group (9.75 mmol/40 min) was significantly higher ( $p < 0.05$ ) during saline infusion than in the normotensive group (5.12 mmol/40 min)

PRC and PAC were significantly correlated in both the hypertensive ( $\rho = 0.72$   $p < 0.01$ ) and the normotensive group ( $\rho = 0.80$   $p < 0.01$ ) before but not after sodium loading

The rise in urinary sodium excretion during sodium loading in the hypertensive patients was significantly correlated with the suppression of PAC ( $\rho = 0.59$   $p < 0.05$ ) but not with the fall in PRC. Changes in urinary sodium excretion in the normotensive subjects were not correlated with changes in PAC or PRC

Discussion and conclusion

The results indicate that the suppressibility of the renin-aldosterone system by hyperosmotic saline is normal in young patients with mild essential hypertension. The disagreement with other studies which showed an abnormal aldosterone secretion pattern during sodium loading could be attributed to differences in the amount of sodium given, the manner and duration of loading and to the fact that many patients studied previously were older and suffered from more pronounced hypertensive vascular disease (2). The rise in urinary sodium excretion with decreasing PAC suggests that PAC might be a regulatory factor in exaggerated natriuresis in young patients with mild essential hypertension.

Reference

1. Giese J, Jørgensen M, Nielsen M D, Lund J O & Munck O  
Plasma renin concentration measured by use of radioimmunoassay for angiotensin II. Scand J clin Lab Invest 26:355 1970



- 2 Pedersen E B & Kornerup, H J : The renin-aldosterone system in exaggerated natriuresis of essential hypertension Clin Sci Mol Med 53:573 1977
- 3 Rask-Madsen, J Bruusgaard A Munck O Nielsen, M D & Worning, H : The significance of bile acid and aldosterone for the electrical hyperpolarization of the human rectum in obese patients treated with intestinal by-pass operation Scand J Gastroent 9: 417, 1974

DIFFERENT ARTERIOLAR DIAMETER IN DOCA-HYPERTENSIVE AND POST-DOCA  
HYPERTENSIVE RATS ESTIMATED BY MEANS OF MICROSPHERES

L. Mørkrid B.M. Iversen and J. Øfstad  
Medical Department A University of Bergen Norway

The main intent of this study was to estimate afferent arteriolar diameters ( $d_{AA}$ ) in 4 different groups of male albino Wistar rats: normal controls, heminephrectomized controls, DOCA NaCl hypertensive rats and post-DOCA hypertensive rats

**MATERIAL AND METHODS**

The animals were fed on standard pellets. The hypertension was induced by the subcutaneous implantation of 75 mg desoxycorticosteroneacetate (DOCA) and substituting drinking water with 1% of NaCl in water. These animals were studied 53 - 211 (mean 111) days after the implantation. Heminephrectomy and DOCA-implantation were done in ether narcosis. In the post-DOCA group the DOCA-pellet was removed 119 days after implantation and in the following 16 days until the microspheres were injected the 1% of NaCl was substituted with ordinary tap water. The systolic blood pressure was measured with regular intervals by means of a tail cuff. The DOCA-hypertension started to develop in about 20 days with a slow further increase in the blood pressure until a stable niveau was reached about 50 - 60 days after implantation of the DOCA-pellet.

A specially designed microsphere diameter distribution was obtained after repeated sedimentation in water of two stock solutions with nominal diameters  $15 \pm 3$  and  $25 \pm 5 \mu\text{m}$ . A small sample of  $^{141}\text{Ce}$ -labelled  $15 \mu\text{m}$  microspheres was added. The diameters ranged from 10 to  $35 \mu\text{m}$  in the final solution. Prior to injection the suspension was vigorously shaken and ultrasound was used to break aggregates between the microspheres.

The animals were anaesthetized with an intraperitoneal injection of Nembutal Natrium<sup>®</sup> (50 mg/kg) and the trachea was cannulated. Systemic arterial blood pressure was measured via a PE-50 catheter introduced through the left common carotid artery and advanced to the aortic arch. This catheter which had its distal end sealed off and was supplied with circumferential sideholes was also used for the injection of the microspheres (injection time 10 - 15 s). Renal blood flow (RBF) was measured by the reference sample technique.

- 2 Pedersen,E B & Kornerup H J : The renin-aldosterone system in exaggerated natriuresis of essential hypertension Clin Sci Mol Med 53:573,1977
- 3 Rask-Madsen,J Bruusgaard A ,Munck □ Nielsen M □ & Worning, H : The significance of bile acid and aldosterone for the electrical hyperpolarization of the human rectum in obese patients treated with intestinal by-pass operation Scand J . Gastroent 9: 417,1974

The heminephrectomized animals had a lower body weight and a significantly higher kidney weight ( $P < 0.001$ ) than the normal controls but blood pressure RBP and  $d_{AA\ dist}$  were not significantly different. The systolic blood pressures (SAP) in DOCA-NaCl hypertension and in post DOCA hypertension were not significantly different during the experiment but a significant increase had taken place when comparing with the normal and heminephrectomized controls ( $P < 0.005$ ). The renal blood flows were not significantly different for any of the four groups.

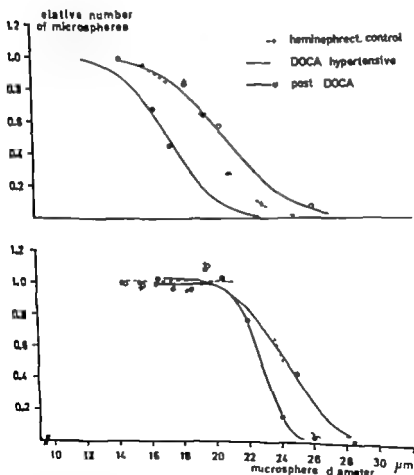


Figure 1 Relative entrance of microspheres into glomeruli (upper panel) and into afferent arterioles (lower panel) as a function of microsphere diameter. The curves for the normal control (not shown here) were lying close to those of the heminephrectomized control.

A reference blood flow of 10  $\mu\text{l/s}$  was withdrawn for about 45 s through a PE-10 catheter placed in one femoral artery. The systemic circulation was abruptly stopped by the intravenous injection of concentrated KCl at about 70 - 90 s after the microsphere injection was started. The kidneys were removed weighed put in 4% formaline in phosphate buffer and the radioactivity was counted in a well counter. Tissue sections of 30  $\mu\text{m}$  thickness were stained with hematoxylin-eosin and mounted for microscopical examination. The maximal visible diameter of the microspheres as well as their anatomical positions (glomerular in afferent arterioles in interlobular arteries) were recorded. The relative number of microspheres entering the afferent arterioles and the relative number of microspheres passing from afferent arterioles into the glomeruli were calculated as a function of microsphere diameter (Figure 1). These curves were calculated uncorrected and when correcting for section thickness (1). The mean values and the standard deviations in the diameter distributions of the proximal and the distal part of the afferent arterioles were then estimated by means of nonlinear regression analysis of these microsphere entrance curves (2). In addition the flow conductance ratio (FCR) relative to the normal controls was calculated.

## RESULTS AND DISCUSSION

Table 1 Experimental data. Values denoted by an † are corrected for section thickness (mean  $\pm$  SEM)

	Normal controls	Heminephrect controls	DOCA-NaCl hypertensive	post-DOCA hypertensive
No. of rats	4	5	6	5
(8 kidneys)				
Body wt (g)	317 $\pm$ 11	253 $\pm$ 19	308 $\pm$ 19	322 $\pm$ 17
Kidney wt (g)	98 $\pm$ 03	1.43 $\pm$ 06	2.39 $\pm$ 19	2.05 $\pm$ 12
SAP (mmHg)	154 $\pm$ 4	156 $\pm$ 9	219 $\pm$ 10	210 $\pm$ 11
RBF (ml/min/g)	2.73 $\pm$ 23	3.27 $\pm$ 69	2.90 $\pm$ 53	2.94 $\pm$ 47
$d_{AA}$ dist ( $\mu\text{m}$ )	19.3 - 19.2†	19.8 - 20.3†	17.0 - 17.4†	20.5 - 20.8†
	1.00	1.05 - 1.16†	61 - 65†	1.28 - 1.36†

The heminephrectomized animals had a lower body weight and a significantly higher kidney weight ( $P < 0.001$ ) than the normal controls but blood pressure RBF and  $d_{AA\ dist}$  were not significantly different. The systolic blood pressures (SAP) in DOCA NaCl hypertension and in post-DOCA hypertension were not significantly different during the experiment but a significant increase had taken place when comparing with the normal and heminephrectomized controls ( $P < 0.005$ ). The renal blood flows were not significantly different for any of the four groups.

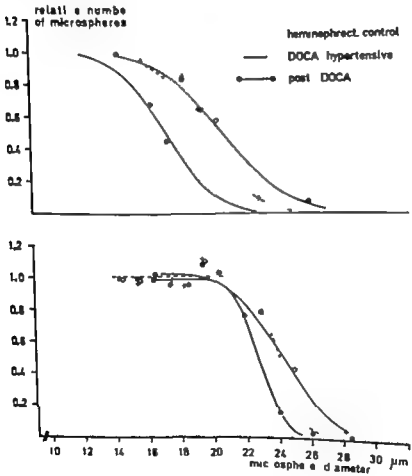


Figure 1 Relative entrance of microspheres into glomeruli (upper panel) and into afferent arterioles (lower panel) as a function of microsphere diameter. The curve for the normal control (not shown here) were lying close to those of the heminephrectomized control. Correction for section thickness (30  $\mu m$ ) has been made.

The most prominent changes were a significantly smaller  $d_{AA \text{ dist}}$  in DOCA-NaCl hypertension than in the normal and heminephrectomized controls ( $P < 0.001$ ) and a significantly larger  $d_{AA \text{ dist}}$  in post-DOCA hypertension than in DOCA-NaCl hypertension. The parameter  $d_{AA \text{ dist}}$  in post-DOCA hypertension was even significantly larger than for the normal and heminephrectomized controls ( $P < 0.05$ ).

Combining this with the flow and pressure data in Table 1 one may conclude that in DOCA-NaCl hypertension the afferent arteriole and especially its distal part is constricted to increase preglomerular resistance and maintain a reasonable glomerular perfusion pressure. In the post-DOCA hypertension one may suggest that the interlobular artery is constricted since we found the afferent arteriole dilated which may be a secondary autoregulatory response. Our findings thus give support to the hypothesis that hypertension induced changes in the interlobular artery reduce the afferent arteriolar perfusion pressure and provoke an autoregulatory dilation of the afferent arteriole. The hypertension is then transformed from a normal renin to a high renin hypertension.

#### REFERENCES

1. Bach, G : Kugelgrößenverteilung und Verteilung der Schnittkreise; ihre wechselseitigen Beziehungen und Verfahren zur Bestimmung der einen aus der anderen. In Symposium on Quantitative Methods in Morphology Wiesbaden 1965 edited by ER Weibel H Elias Berlin 1967 pp 23 - 45
2. Mørkrid L, Ofstad J and Willassen Y : Diameter of afferent arterioles during autoregulation estimated from microsphere data in the dog kidney. Circ Res 42: 181 - 191 1978

SODIUM BALANCE AND STRUCTURAL VASCULAR CHANGES IN THE KIDNEY  
DURING DEVELOPMENT OF HYPERTENSION IN SPONTANEOUSLY HYPERTENSIVE  
RATS

By

Hans Hellitz, Sten Lundin, Sven-Erik Ricksten, Gunna Gethberg,  
Mattias Aréll, Margareta Hildebrand and Gösta Berglund  
From the Department of Medicine I Sahlgrenska Hospital and the  
Department of Physiology University of Göteborg, Sweden

INTRODUCTION

The mechanisms leading to primary hypertension remain and in genetically hypertensive rats are still poorly understood. The spontaneously hypertensive rats (SHR) display signs of increased sympathetic activity (10) while plasma volume is normal or slightly lowered (11). In the Mott hypertensive trait of rats (MHS) the pressure rise is however associated with sodium retention and plasma volume increase (2). In addition, studies in SHR have demonstrated adaptive increases in wall/lumen ratio of the periglomerular resistance vessels leading to increased peripheral resistance in the established phase of hypertension (8). In essential hypertension in man there is evidence of reduced ability to excrete salt and water as well as of an increased arterial stiffness with increasing severity of hypertension (1). Thus both in man and rats the progression of hypertension is accompanied by a inability to handle sodium as well as a gradual increase in renal vascular resistance. The present study was therefore undertaken to investigate if the progressively developing structural vascular changes within the kidney contribute to the impaired renal handling of sodium or if these two factors are independently of each other.

MATERIAL AND METHODS

Experiments were performed on 7 and 16 weeks old spontaneously hypertensive rats (SHR) (10) and matched normotensive control Wistar rats (NCR) Wistar-Kyoto rats (WKR) aged 16 weeks were also used as controls. Each group consisted of 10 rats. At 7 weeks of age SHR had 10-20% higher blood pressure than NCR. This difference increased to around 25% at 16 weeks of age. The animals used in balance studies were placed in individual metabolic cages. After 5 days of adaptation the balance studies were performed during the next ten day period during



The most prominent changes were a significantly smaller  $d_{AA \text{ dist}}$  in DOCA-NaCl hypertension than in the normal and heminephrectomized controls ( $P < 0.001$ ) and a significantly larger  $d_{AA \text{ dist}}$  in post-DOCA hypertension than in DOCA-NaCl hypertension. The parameter  $d_{AA \text{ dist}}$  in post-DOCA hypertension was even significantly larger than for the normal and heminephrectomized controls ( $P < 0.05$ ).

Combining this with the flow and pressure data in Table 1 one may conclude that in DOCA-NaCl hypertension the afferent arteriole and especially its distal part is constricted to increase preglomerular resistance and maintain a reasonable glomerular perfusion pressure. In the post-DOCA hypertension one may suggest that the interlobular artery is constricted since we found the afferent arteriole dilated which may be a secondary autoregulatory response. Our findings thus give support to the hypothesis that hypertension induced changes in the interlobular artery reduce the afferent arteriolar perfusion pressure and provoke an autoregulatory dilation of the afferent arteriole. The hypertension is then transformed from a normal renin to a high renin hypertension.

#### REFERENCES

1. Bach G : Kugelgrößenverteilung und Verteilung der Schnittkreise, ihre wechselseitigen Beziehungen und Verfahren zur Bestimmung der einen aus der anderen. In Symposium on Quantitative Methods in Morphology Wiesbaden 1965 edited by ER Weibel H Elias Berlin 1967 pp 23 - 45
2. Mørkrid L, Ofstad J and Willassen Y : Diameter of afferent arterioles during autoregulation estimated from microspheres data in the dog kidney. Circ Res 42: 181 - 191 1978

SHR aged 16 weeks showed an increased sodium retention only when calculated per g of body weight

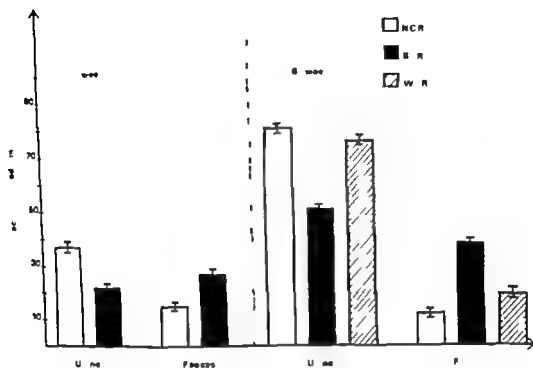


Fig 1 Fractional excretion of sodium by the kidneys and the gastrointestinal tract

Urinary load (once excretion was not significantly different between SHR and NCR at 7 weeks of age but at 16 weeks it was significantly increased in SHR (NCR  $4.5 \pm 0.1$   $\mu\text{mol/day}$  SHR  $9.1 \pm 1.5$   $\mu\text{mol/day}$   $p < 0.05$ ). PRA was significantly lower in SHR aged 16 weeks than in NCR (NCR  $4.5 \pm 0.5$   $\text{ng/ml/h}$  SHR  $1.9 \pm 0.3$   $\text{ng/ml/h}$   $p < 0.05$ ). No statistical analyses were performed at 7 weeks of age due to low number of observations ( $n = 5$ ) but the figure for PRA was lower for SHR versus this age. No significant differences in noradrenaline excretion were found between SHR and NCR at any age.

The hemodynamic effects of structural vessel changes increased resistance to maximal dilation and increased steepness of the resistance curve and an increased maximal pressure response to cardiac output.

sodium excretion were measured. In addition urinary aldosterone and noradrenaline were determined. Body weight was measured every third day. After the balance period the arterial blood pressure was measured in the awake animals via a cannula inserted into the tail artery during brief ether anaesthesia. The rats were then decapitated during a brief ether anaesthesia and blood samples for plasma renin activity (PRA) were collected from the carotid artery. Urinary aldosterone was measured with a radioimmunoassay kit from NEN and urinary noradrenaline was analysed with a modified method according to von Euler and Floding (4). PRA was analysed using a radioimmunoassay for angiotensin I (7).

In separate groups of age-matched SHR and NCR the isolated renal vascular beds were pairwise perfused with an artificial plasma substitute at constant flow while pressure was simultaneously recorded (6). Maximal dilatation was achieved by injections of papaverine. From a level of maximal dilatation graded doses of noradrenaline were administered and steady state pressure was recorded at each dose until the maximal obtainable pressor response had been achieved. Resistance curves were then plotted for each experiment and the differences within each pair concerning 1) resistance at maximal dilatation, 2) steepness of the resistance curve and 3) maximal pressor response were analysed (5). Differences in these parameters indicate the presence of structural vascular changes.

## RESULTS

At 7 weeks of age when the SHR is considered to be in the borderline phase of hypertension urinary sodium excretion was markedly lowered compared to NCR. The sodium intake was slightly lower in the hypertensive animals but this did not fully explain the difference observed in urinary sodium. Faecal sodium was also analysed and higher values were consistently found in SHR compared to NCR. The same pattern was seen in SHR aged 16 weeks both compared to NCR and to WKR. At this age SHR is considered to be in the phase of early established hypertension. To study the fate of ingested sodium fractional excretion was calculated as percentage of the respective intakes (Fig 1) (8). These figures clearly indicate that there is a shift in excretion of sodium from the kidneys to the gastrointestinal tract in SHR both at 7 weeks and 16 weeks of age. Young SHR did not show any significant sodium retention or sodium retention per gram body weight increase compared to NCR.

# REFERENCES

- 1 Berglund G Wikstrand J Ljungma S Hartford M and Wilhelmsson L : Sodium excretion and sympathetic activity in relation to severity of hypertension *Contr Nephrol* 8:134 1977
- 2 Bianchi G Bae P G Fox U Duzi L Pagetti D and Giovanetti A M : Changes in renin water balance and sodium balance during development of high blood pressure in genetically hypertensive rats *Circ Res suppl* 1 1975 p 1153
- 3 Dillon G F : The role of regulation of renal tubular sodium reabsorption *Am J Physiol* 233 F73 1977
- 4 von Euler U S and Floding I : Diagnosis of pheochromocytoma by fluorometric titration of adrenaline and noradrenaline in plasma *Scand J Clin Lab Invest* 8:288 1956
- 5 Folkow B Hallbäck M Lundgren Y and Weiss L : Background of increased flow resistance and vascular reactivity in spontaneously hypertensive rats *Acta Physiol Scand* 80-93 1970
- 6 Folkow B Hallbäck M Lundgren Y and Weiss L : Resistance in spontaneously hypertensive rats *Acta Physiol Scand* 83:90 1971
- 7 Giese J Jørgensen M Nielsen M D Lund J O and Munk B : Plasma renin concentration measured by use of radioimmunoassay for angiotensin I *Scand J Clin Lab Invest* 26:355 1970
- 8 Göthberg G Hallbäck M Lund S Ricksten S E and Folkow B : A comparison of renal flow resistance in normotensive controls and spontaneously hypertensive rats (SHR) *Clin Exp Pharmacol* suppl 3 1976 p 79
- 9 Møhlig J and Møhlig B : Evaluation of sodium and potassium balance in rats *J Appl Physiol* 33:688 1977
- 10 Okamoto K : Spontaneous hypertension Tokyo Igaku Shoin Ltd 1972
- 11 Rippe B Lund S and Folkow B : Blood volume plasma volume and transcapillary escape of albumin in young SHR and MCR *Clin Exp Hypertension* 1 pre 1978
- 12 Wong O and Metcalf-Gibson A : The electrolyte content of faeces *Proc R Soc Med* 58:1007 1965

evident with increasing age and severity of hypertension in SHR. Thus at 7 weeks of age when the blood pressure increase in SHR was only of the order of 10% only maximal pressor response was enhanced implying an increased bulk of contractile tissue of the resistance vessels. At 16 weeks of age also an increased steepness of the resistance curve was evident indicating an increased wall/lumen ratio of the resistance vessels of the renal vascular bed in SHR.

### DISCUSSION

A consistent finding of the present study is a shift of the sodium excretion from the renal to the gastrointestinal route in SHR. The increased aldosterone level in SHR could hardly contribute to this shift since this hormone is suggested to have similar effects on both sites (12). The reduced PRA values in 16 weeks old SHR indicate that the aldosterone could be mediated via central hypophyseal influences and thus be a consequence of the increased central neuro-hormonal control in SHR (10). The increased sodium retention per gram body weight increase in SHR aged 16 weeks might in part be due to an altered growth pattern in older SHR and does not seem to contribute to the development of hypertension since it was not present in young prehypertensive SHR.

The present study thus illustrates that structural vascular changes within the kidney develop progressively with the aggravation of hypertension in SHR but that renal sodium excretion is reduced already in young prehypertensive SHR. However, the reduced renal ability to excrete sodium is compensated by an enhanced fecal sodium excretion so that no difference in sodium retention could be detected in the youngest animals. This observed shift in sodium excretion might be caused by a primary abnormality within the gastrointestinal tract and/or of its nervous control so that less sodium is absorbed. An alternative explanation is that SHR exhibit a reduced renal ability to excrete sodium already in the prehypertensive phase when structural vascular changes only partially contribute to the increased renal vascular resistance. Furthermore since an increased sympathetic activity seems to greatly contribute to the development of SHR hypertension an increased sympathetic control might increase sodium reabsorption in SHR via a nervous control of the proximal tubular cells (3). It is therefore concluded that the observed shift in sodium balance in young SHR is not primarily due to a structurally increase in renal vascular resistance but may be due to an altered nervous control of the kidney and its vascular bed and/or of the gastrointestinal tract.

patients the blood pressure in the upper half of the body had fallen to some extent during the follow up period and at the follow up study 11 patients had a blood pressure measured with the ordinary cuff method below 140/90. 3 had pressure between 140/90 and 160/95 and one had a blood pressure exceeding the last limit.

The patients operated on for aortic coarctation were compared to four different groups of either normotensive individual or hypertensive patients studied with the same technique. Sixteen patients (H) have a moderate hypertension (mean age 43 years) (9). Another 16 individuals are normotensive control (HC) matched to the above mentioned hypertensive individuals for sex, age, length and weight (mean age 44 years) (9). The reference material also includes 44 young men (mean age 20 years) with a mild blood pressure elevation (B; borderline group) and 29 normotensive male controls (BC) of the same age (mean age 19 years) (11). No individual in this study was on antihypertensive medication at the time of examination. Three hypertensives had previously received small doses of blood pressure lowering drugs (beta blockers, hydralazine or saluretic) but all these drugs were withdrawn at least 24 hours before the study was done.

### Methods

Blood pressure at rest is recorded intraarterially through a catheter in the right brachial artery (in the reference groups usually in the left brachial artery). Hand blood flow is recorded plethysmographically from the lectically damped mean arterial blood pressure and the simultaneously measured blood flow, recorded from the catheterized side blood flow resistance is calculated. Blood pressure and blood flow is recorded under function 1 vasomotor nerve blockade induced by general heating of the patient as well as under maximal vasodilatation. Maximal vasodilatation is induced by a combination of general heating of the patient, local heating of the hands, arterial occlusion and hand muscle work until exhaustion. This combination of vasodilating stimuli induces an almost complete relaxation of the smooth muscle cells in the resistance vessels of the hands (9).

### Results

The results are summarized in Fig. 1 which shows traces of mean blood pressure at rest and blood flow resistance in the hand under maximal vasodilatation of the coarctation group (CA) and for the borderline group. Mean values for the groups and standard error of the means are presented. It can be seen that the coarctation group has a mean blood pressure equaling that in the borderline group (CA: 93.7 and B: 93.2 mm Hg) tending to be

# Hemodynamic signs indicating structural vascular changes of hypertensive type after surgery for aortic coarctation

by

R. Silvertsson, E. Hansson and E. Eriksson

Department of Clinical Physiology II, Department of Pediatric Surgery and Department of Pediatrics, University of Göteborg, Göteborg, Sweden

Prior to the introduction of operative treatment of aortic coarctation the prognosis of this disease was bad. The patients usually died in complications to hypertension in the upper part of the body like intracranial haemorrhages, rupture of major vessels or of collaterals or congestive heart failure (1). After surgery has been introduced in the treatment of these patients the prognosis has improved considerably, but it has probably not been normalized since recent reports indicate a remaining elevated cardiovascular mortality in these patients (2). A number of studies also indicate a remaining slight blood pressure elevation in many of these patients in spite of a good anatomical result (2, 3, 4, 5).

Previous studies on patients with established hypertension and borderline hypertension indicate the existence of hemodynamically important structural changes in the resistance vessels of these individuals (6, 7, 8, 9). The aim of this study is to see whether or not structural vascular changes could be tracked in the vascular beds of a group of young men operated on for aortic coarctation about ten years previously. The existence of such changes might indicate a vascular fault remaining after the previous hypertension.

## Material

The actual investigation is one part of a hemodynamic follow up study in patients operated on for aortic coarctation during the years 1958-1974 at the Children's Hospital in Gothenburg. Of the patients operated on during this period 69 are still alive. From this group 19 young symptom-free men were selected for a hemodynamic study which included among other things intraarterial blood pressures proximal and distal to the previous coarctation and cardiac output determinations. The measurements were done at rest and during physical exercise. The data from this study will be published separately (10). Of these patients studied hemodynamically 10 patients agreed to participate in the actual study of the peripheral hemodynamic situation. The age of these 10 patients varied between 16 and 23 years (mean 21 years). The age at the operation ranged between 6 and 13 years (mean 10 years) and between 7 and 16 years (mean 11 years) had passed since the operation. In all these

patients the blood pressure in the upper half of the body had fallen to some extent during the follow up period and at the follow up study II patients had a blood pressure measured with the ordinary cuff method below 140/90. 3 had a pressure between 140/90 and 160/95 and one had a blood pressure exceeding the last limit.

The patients operated on for aortic coarctation are compared to four different groups of either normotensive individual or hypertensive patients treated with the same technique. Sixteen patients (H) have a moderate hypertension (mean age 43 years) (9). Another 16 individuals are normotensive controls (HC) matched to the above mentioned hypertensive individual for sex, age, length and weight (mean age 44 years) (9). The reference material also includes 44 young men (mean age 20 years) with a mild blood pressure elevation (B "border line group") and 29 normotensive male controls (BC) of the same age (mean age 19 years) (11). No individual in this study was on antihypertensive medication at the time of examination. These hypertensives had previously received small doses of blood pressure lowering drugs (beta nidi, deserpi, hydralazine or saluretics) but all these drugs were withdrawn at least 24 hours before the study was done.

#### Method

Blood pressure at rest is recorded intrarterially through a catheter in the right brachial artery (in the reference groups usually in the left brachial artery). Hand blood flow is recorded plethysmographically. From the electrically damped mean intrasystolic blood pressure and the simultaneously measured blood flow recorded from the catheterized side blood flow resistance is calculated. Blood pressure and blood flow is recorded under functional vasomotor nerve blockade induced by general heating of the patient, well as under maximal vasodilatation. Maximal vasodilatation is induced by a combination of general heating of the patient, local heating of the hand, intraligamentary occlusion and hand muscle work until exhaustion. This combination of vasodilating stimuli induces an almost complete relaxation of the smooth muscle cells in the resistance vessels of the hands (9).

#### Results

The results are summarized in Fig. 1 which shows intrarterial mean blood pressure, systolic and blood flow resistance in the hand under maximal vasodilatation for the coarctation group (CA) and for the 4 reference groups. Mean values for the group are standardized for all of the means represented. It can be seen that the coarctation group has a mean blood pressure equaling that of the "border line group" (CA: 93.7 and B: 93.2 mm Hg) tending to be



higher than the pressure in one of the normotensive control groups (BC 86.9 mm Hg not significant) being significantly higher than that in the other normotensive control group (HC  $p < 0.05$ ) and significantly lower than the pressure in the hypertensive group (H; 122.1 mm Hg  $p < 0.001$ ). On the other hand blood flow resistance at maximal vasodilatation is as high in the coarctation group as in the hypertensive group (2.74 and 2.48 respectively not significant) far exceeding the resistances in the borderline group (2.02  $p < 0.02$ ) and the normotensive control groups (BC 1.96  $p < 0.01$  and HC 1.67  $p < 0.01$ ). The resistance at maximal dilatation is however not increased in relation to the blood pressure in all coarctation patients. In three of them there is a normal relation between resistance at maximal dilatation and resting mean blood pressure i.e. the same as in the reference groups.

### Discussion

The method used for determination of resistance at maximal dilatation in this study is mainly the same as the one previously described (9, 10) but the resistance is here determined in the catheterized side instead of the non catheterized one. This is true also for the reference groups. It is due to the fact that the left subclavian artery is often obstructed to some extent after surgery for aortic coarctation due to technical reasons and therefore both blood pressure and blood flow has to be determined on the right side in the coarctation group. The fact that blood flow is measured in the same arm as the blood pressure might influence the results to some extent since the catheter often reduces blood flow a little. However since blood flow resistances used in this study for the reference groups are recalculated from the previous studies (9, 10) using data from the catheterized side the error introduced by the catheter should apparently affect the different groups equally.

Furthermore the method used in the coarctation group as well as in the borderline group (B) and in the corresponding normotensive control group (BC) (10) differs from the one used in the hypertensive group (H) and in its corresponding normotensive control group (HC) (9) so far that the period of indirect heat was longer in the latter groups. This fact might explain the slight difference in resistance between the two normotensive groups (HC and BC).

The resting intraarterial mean blood pressure was only marginally elevated in the coarctation group and elevated to the same level as in the borderline group. This is in agreement with our observations in the whole patient

material investigated with central hemodynamics (10). In that study a blood pressure elevation, mainly affecting the systolic blood pressure was recorded in the right arm in most patients with a normal or low systolic pressure. In the right leg both at rest and during physical exercise. A blood pressure difference between the upper and lower body half was usually found, particularly during exercise. The observed blood pressure elevation in the upper body half of these 10 patients is also in agreement with the findings by others (2, 3, 4, 5).

In spite of a significant elevation of the mean brachial artery blood pressure in the coarctation group, blood flow resistance at maximal vasodilatation considerably increased. The mean value for the coarctation group is of the same magnitude as the mean value for the patients with established hypertension (H). The elevated resistance at maximal vasodilatation indicates that the resistance vessels in the hand and probably in the whole upper body half are structurally changed in the same way as the resistance vessels of patients with established hypertension seem to be. This is in agreement with observations by Šamáněk et al. (12). It is most likely that these structural changes are secondary to the preoperative elevation of the blood pressure in the upper half of the body. The fact that the vascular changes as indicated by the high resistance to maximal dilatation are much more pronounced than should be expected from the blood pressure elevation may be explained by a combination of a certain blood pressure fluctuation operation and a incomplete or lacking reversibility of these changes. This is in agreement with our previous findings in hypertensive patients treated with blood pressure lowering drugs (13).

Thus these results indicate that the structural change of the resistance vessels of patients with high blood pressure is at least partially irreversible in spite of a pronounced blood pressure reduction of long duration in young individuals. Furthermore the fact that the vascular changes seem to be at least incompletely reversible is a argument for a early blood pressure lowering therapy operative and/or pharmacological in patients with aortic coarctation.

86.9 mm Hg not significant) being significantly higher than that in the other normotensive control group (HC  $p < 0.05$ ) and significantly lower than the pressure in the hypertensive group (H 122.1 mm Hg  $p < 0.001$ ). On the other hand blood flow resistance at maximal vasodilatation is as high in the coarctation group as in the hypertensive group (2.74 and 2.48 respectively not significant) far exceeding the resistances in the borderline group (2.02  $p < 0.02$ ) and the normotensive control groups (BC; 1.96;  $p < 0.01$  and HC 1.67  $p < 0.01$ ). The resistance at maximal dilatation is however not increased in relation to the blood pressure in all coarctation patients. In three of them there is a normal relation between resistance at maximal dilatation and resting mean blood pressure i.e. the same as in the reference groups.

### Discussion

The method used for determination of resistance at maximal dilatation in this study is mainly the same as the one previously described (9, 10) but the resistance is here determined in the catheterized side instead of the non catheterized one. This is true also for the reference groups. It is due to the fact that the left subclavian artery is often obstructed to some extent after surgery for aortic coarctation due to technical reasons and therefore both blood pressure and blood flow has to be determined on the right side in the coarctation group. The fact that blood flow is measured in the same arm as the blood pressure might influence the results to some extent since the catheter often reduces blood flow a little. However since blood flow resistances used in this study for the reference groups are recalculated from the previous studies (9, 10) using data from the catheterized side the error introduced by the catheter should apparently affect the different groups equally.

Furthermore the method used in the coarctation group as well as in the borderline group (B) and in the corresponding normotensive control group (BC) (10) differs from the one used in the hypertensive group (H) and in its corresponding normotensive control group (HC) (9) so far that the period of indirect heat was longer in the latter groups. This fact might explain the slight difference in resistance between the two normotensive groups (HC and BC).

The resting intraarterial mean blood pressure was only marginally elevated in the coarctation group and elevated to the same level as in the borderline group. This is in agreement with our observations in the whole patient

## References

- 1 Campbell M : Natural history of coarctation of the aorta Brit Heart J 32 633 1970
- 2 Maron B J Humphries J D Rowe R D & Mellett E D : Prognosis of surgically corrected coarctation of the aorta A 20-years post operative appraisal Circulation 47 119 1973
- 3 Chiariello L Agosti J & Subramanian S : Coarctation of the aorta in children and adolescents : surgical treatment and review of 120 patients Chest 70 621 1976
- 4 Kanton M A & Olley P M : Residual hypertension after coarctectomy in children Amer J Cardiol 37 769 1976
- 5 Shinebourne EA Tan A S Y Elseed A H Paneth M Lennox S H Cleland W P Lincoln C Joseph M C & Anderson R M Coarctation of the aorta in infancy and childhood Brit Heart J 38 375 1976
- 6 Conway J : A vascular abnormality in hypertension A study of blood flow in the forearm Circulation 27 520 1963
- 7 Folkow B Structural myogenic humoral and nervous factor controlling peripheral resistance I Hypotensive Drugs ed by M Harington Munksgaard Press London 163 1956
- 8 Folkow B Grimby G & Thulesius O Adaptive structural changes of the vascular walls in hypertension and their relation to the control of the peripheral resistance Acta physiol scand 44 255 1958
- 9 Sivebsson R The haemodynamic importance of structural vascular changes in essential hypertension Acta physiol scand suppl 343 1 1970
- 10 Hansson E & Eriksson B O Cardiac output and treatment of blood pressure at rest and during exercise after surgery for coarctation of the aorta To be published
- 11 Sivebsson R Sannerstedt R & Lundgren Y Evidence for peripheral vascular involvement in mild elevation of blood pressure in man Clin Sci Mol Med 51 65 1976
- 12 Zamánek M Goetzová J Flisová J & Skovránek J Differences in muscle blood flow in upper and lower extremities of patients after coarctation of the aorta Circulation 54 3 377 1976
- 13 Sivebsson R Peripheral haemodynamic in essential hypertension Acta med scand suppl 606 43 1977

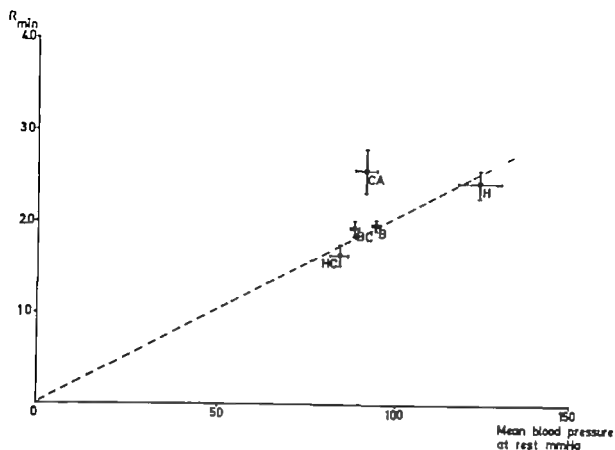


Fig 1 Intraarterial mean blood pressure at rest and blood flow resistance in the hand at maximal vasodilatation ( $R_{min}$ ) in the coarctation group (CA) and in the four reference groups the hypertensive group (H) and the corresponding normotensive control group (HC) the "border line group" (B) and its normotensive control group (BC) are shown. Mean values for the groups and standard errors of the means are given.

## RESULTS

Nine of the patients had stenosis in the main stem of the renal artery 4 patients bilaterally and 5 unilaterally One of the patients with unilateral stenosis was investigated haemodynamically on the nonstenotic side His kidney has therefore been regarded as a kidney without arterial stenosis Of the remaining 8 kidneys with arterial stenosis one was due to arteriosclerosis and 7 to fibromuscular hyperplasia

Of the kidneys without arterial stenosis 3 were normal and contralateral to a hypoplastic kidney 3 comprised a normal kidney to a normal kidney One was a hypoplastic kidney and two kidneys had small areas of cortical reduction

### Blood pressure

MAP before induction of the block in the group with renal artery stenosis was  $136 \pm 18$  (S D) and after the block  $126 \pm 22$  (S D) mmHg In the group without stenosis the MAP changed from  $102 \pm 16$  (S D) to  $91 \pm 19$  (S D) mmHg

### Renal blood flow

In the kidneys without arterial stenosis a negative linear correlation was found between MAP and flow ( $r=0.77$ ;  $p < 0.01$ ) before the splanchnic block In kidneys with arterial stenosis there was no significant correlation After the block no correlation was found in either group Before the splanchnic block the percentual proportion of the total blood flow in compartment 1 was linearly correlated to the MAP This was true both for kidneys with arterial stenosis ( $r=0.87$ ;  $p < 0.01$ ) and for those without ( $r=0.87$ ;  $p < 0.01$ ) Thus at a high arterial pressure compartment 1 constituted a smaller proportion of the blood flow than at a lower pressure After the block there was no significant correlation

### Renal vascular resistance

A positive linear correlation was found between renal vascular resistance and mean arterial pressure in both groups The

# THE EFFECT OF SPLANCHNIC BLOCK ON RENAL HAEMODYNAMICS AND RENIN PRODUCTION IN HYPERTENSIVE PATIENTS

C Mårin L-E Löfrelius P-O Löfroth L Wide L Wiklund & H Åberg

From the Departments of Internal Medicine Diagnostic Radiology  
Clinical Chemistry and Anaesthesiology University Hospital Uppsala  
Sweden

## INTRODUCTION

The secretion of renin in the kidney is regulated by three different but more or less interactive mechanisms namely the sympathetic nervous system the renal baroreceptors and the sodium concentration in the macula densa (1) In an attempt to be able to better define the indications for surgical therapy in patients with renal artery stenosis the role of the sympathetic nervous system was evaluated by studying the effect of splanchnic block on the secretion of renin and on renal haemodynamics The investigation was carried out in connection with nephroangiography

## PATIENTS AND METHODS

Eighteen patients - 4 men and 14 women of ages 21 - 63 years with hypertension of suspected renovascular origin were studied The patients were strictly requested not to take any anti-hypertensive drug during the four weeks preceeding the investigation The patients attended the hospital one week before the investigation and the last five days preceeding the examination they were given a low sodium diet (approximately 20 mmol  $\text{Na}^+$ /day) and 40 mg furosemide (Lasix<sup>R</sup>) daily

On the day before the examination a polyethylene catheter was inserted into the patients back until its tip lay close to the splanchnic nerves at the level of the anterior margin of the first lumbar vertebra

On the day of investigation a catheter was inserted through the femoral artery for renal angiography and renal blood flow determination by the Xenon - 133 wash-out method (4 5) Blood samples were collected from both renal veins for subsequent analysis of the plasma renin activity The mean arterial pressure (MAP) was intermittently recorded proximal to the stenosis if such existed The splanchnic block was then induced with 40 ml 0.25% plain bupivacaine (Marcaine) injected via the catheter inserted on the previous day After the splanchnic block renal blood flow determination and blood sampling from

and this may indicate that compartment 1 is a distribution volume whose size is dependent on the sympathetic tone. It has been shown that a decrease in blood pressure leads to an increase of PRA (3). This rise in PRA could be due to a stimulated sympathetic activity or due to baroreceptor function. In our study where the sympathetic activity was eliminated by splanchnic block, a decrease of the MAP and PRA was obtained. Furthermore, a significant correlation was found between the relative change in PRA and the relative change in renal vascular resistance. The splanchnic block most likely inhibits renin secretion and decreases renal vascular resistance independently. This is supported by the findings of Richardson (7).

In conclusion, there is no significant difference between kidneys with arterial stenosis and those without with respect to the regulation of the haemodynamics. The sympathetic system is of decisive importance for the release of renin from kidneys of patients with hypertension and this system seems to dominate over the baroreceptors at the pressure levels investigated regardless of whether there is a renal artery stenosis or not.



splanchnic block caused a decrease of the renal vascular resistance but there was still a positive linear correlation between renal vascular resistance and MAP

### Plasma renin

Plasma renin activity (PRA) in peripheral vein after 1 hour a rest supine before and after a low sodium diet (approx 20 mmol Na/d) and stimulation with 40 mg furosemide per day changed in patients with renal artery stenosis mean PRA from 1.88 to 4.14 ug/l/h and in patients without stenosis from 1.80 to 9.10 ug/l/h. For evaluating the effect of the splanchnic block on PRA value in renal venous blood the material was divided into three groups. Thirteen kidneys with arterial stenosis showed a significant decrease of the PRA in renal venous blood after the block ( $m=19.5$  to  $13.7$  ug/l/h;  $p < 0.05$ ) and the same was found for six kidneys with parenchymal affection ( $m=22.7$  to  $12.2$  ug/l/h;  $p < 0.05$ ). No significant decrease of PRA was noted in normal kidneys ( $m=17.5$  to  $16.6$  ug/l/h).

Renal renin secretion rate did not allow firm conclusions (6)

### Renin and renal haemodynamics

Only one significant correlation was found namely between the relative change in PRA  $\Delta PRA\%$  and the relative change in renal vascular resistance  $\Delta R\%$  in kidneys with arterial stenosis

### DISCUSSION

The reduction of MAP in this investigation was of the same magnitude as previously found following splanchnic block (8). In our study the splanchnic block caused a decrease of the renal vascular resistance both in patients with renal artery stenosis and those without. The decrease was most pronounced in patients with high initial resistance. A reduction of the relative proportion of the flow in compartment 1 has been reported earlier in patients with hypertension (2). In our investigation this correlation was also found in kidneys with arterial stenosis. After the block no such correlation existed

## THE EFFECT OF HYPERTENSION ON THE MECHANOCARDIOGRAPHIC AND ELECTROCARDIOGRAPHIC MEASUREMENTS.

M. Rajasalmi O Ollinki and J Takkanen Cardiovascular Division  
Department of Internal Medicine University of Oulu Oulu Finland

Left ventricular hypertrophy and heart insufficiency are the most common consequences of arterial hypertension. Both of these affect the mechanocardiographic and electrocardiographic measurements (7-8). Without these pathological states an active cardiac contribution to hypertension has been proposed and its effects on systolic time intervals shown (2-4-5). This effect has been studied in the present study in connection with electrocardiographic data for to get basis for the follow up studies of a cohort of male pulp mill workers.

### Population and methods:

759 male workers were studied. A diastolic blood pressure of 110 mmHg or more was found in 25 men that were not using any cardioactive medication. They formed Group III. Group I consisted of 25 randomly elected but age matched men with diastolic blood pressure of 95 mmHg or less and to Group II were designated 25 men with a diastolic blood pressure from 96 to 109 mmHg. No one had any valvular heart disease or was using any cardioactive medication.

Apex cardiogram, heart sounds and carotid pulse curve were registered with ECG as described before (6). A separate ECG registration was made by Olli 5000 ECG Acquisition, Communication and Analysis System that provide a computer analysis of conventional 12 lead ECG and also the Frank vector loops and maximal spatial vector of QRS (3).

Blood pressure was measured with a mercury sphygmomanometer using as diastolic endpoint the disappearance of Korotkoff voices.

## REFERENCES

- 1 Davis J O The control of renin release In Laragh J H Hypertension Manual Yorke Medical Books Dun-Donelley New York 1974 pp 163 - 196
- 2 Hollenberg N K & Adams D F ; The renal circulation in hypertensive disease Amer J Med 60 773 1976
- 3 Kaneko Y Ikeda T Takeda T & Ueda H : Renin release during acute reduction of arterial pressure in normotensive subjects and patients with renovascular hypertension J Clin Invest 46 705 1967
- 4 Ladefoged J : Measurement of the renal blood flow in man with the <sup>133</sup> Xenon wash-out technique Scand J Clin Lab Invest 18 299 1966
- 5 Lörelius L -E LÖfroth F -O Mörlin D Wiklund L & Åberg H : Renal haemodynamics before and after splanchnic block in patients with hypertension To be published in Scand J Clin Lab Invest
- 6 Lörelius L -E Mörlin D Wide L Wiklund L & Åberg H : The effect of splanchnic block on renin production and renal haemodynamics in hypertensive patients Submitted for publication
- 7 Richardson D Stella A Leonetti G Bartorelli A & Zanchetti A : Mechanisms of renal release of renin by electrical stimulation of the brain stem in the cat Circ Res 34 425 1974
- 8 Wiklund L : Postoperative hepatic blood flow and its relation to systemic circulation and blood gases during splanchnic blockade on fentanyl analgesia Acta anaesthesiol Scand Suppl 58 5 1975

## THE EFFECT OF HYPERTENSION ON THE MECHANOCARDIOGRAPHIC AND ELECTROCARDIOGRAPHIC MEASUREMENTS

M. Rajasaari, M. Ollinki and J. Takkunen Cardiovascular Division  
Department of Internal Medicine University of Oulu Oulu Finland

Left ventricular hypertrophy and heart insufficiency are the most common consequences of arterial hypertension. Both of these affect the mechanocardiographic and electrocardiographic measurements (7, 8). Without these pathological states an active cardiac contribution to hypertension has been proposed and its effects on systolic time intervals shown (2, 4, 3). This effect has been studied in the present study in connection with electrocardiographic data for to get basis for the follow up studies of a cohort of male pulp mill workers.

### Population and methods:

759 male workers were studied. A diastolic blood pressure of 110 mmHg or more was found in 25 men that were not using any cardioactive medication. They formed Group III. Group I consisted of 25 randomly selected but age matched men with diastolic blood pressure of 95 mmHg or less and to Group II were designated 25 men with a diastolic blood pressure from 96 to 109 mmHg. No one had any valvular heart disease or was using any cardioactive medication.

Apex cardiogram, heart sounds and carotid pulse curve were registered with ECG as described before (6). A separate ECG registration was made by Olli 5000 ECG Acquisition, Communication and Analysis System that provide a computer analysis of conventional 12 lead ECG and also the Frank vector loops and maximal spatial vector of QRS (3).

Blood pressure was measured with a mercury sphygmomanometer using as diastolic endpoint the disappearance of Korotkoff voices.

## Results and discussion:

The blood pressure values of all men in Groups I - III were compared to data of same subjects measured 7 years before by the same examiner. In the Groups II and III there was a statistically significant elevation of both systolic and diastolic blood pressures (paired t-test  $p < 0.01$ ). Group I was in the same range than 7 years before as well as the 133 men who had got medication for the treatment of hypertension.

The differences in QS2, PEP and PEP/LVET values as well as the differences in maximal spatial vectors in each group is presented in Table I. The STI values are higher in Group I and III than in Group II. The difference between Group I and III is statistically significant. This is in accordance with previous results from the same factory population (6). The maximal spatial vectors did not differ between the groups but there was a good correlation between left ventricular hypertrophy found by visual reading (Minnesota code 3-1 and 3-3) and the spatial QRS vector that was evidently higher in these men. In group I that means men with normal blood pressure was found 8 men with ECG consistent with the criteria of left ventricular hypertrophy. In Group II there was 6 and in Group III 7 men with the same electrocardiographic diagnosis. This means that the visual interpretation or the use of spatial vector do not separate hypertensive patients on the basis of left ventricular hypertrophy from normal people. The QRS and T vectors in the frontal plane were in the normal range among all subjects examined.

The lengthening of the STI values must be interpreted to signify a lengthening of the ventricular activation and pressure generation (4, 5, 6). The heart needs more time to reach the diastolic pressure and to open the aortic valve and this is seen in the

prolongation of PEP These findings are in accordance with experimental and clinical studies but all investigations have not confirmed them (1-7)

Table 1 Systolic time intervals and maximal spatial QRS vectors in the subjects included in the study

		Group I	Group II	Group III
Age		51 $\pm$ 9	48 $\pm$ 8	51 $\pm$ 10
QS2 index (ms)	mean	494.4	500.7	508.5 <sup>(x)</sup>
	SD	18.1	27.8	32.4
PEP index (ms)	mean	113.1	120.2	130.1 <sup>(x)</sup>
	SD	20.2	31.2	27.7
PEP/LVET	mean	0.328	0.362	0.406 <sup>(x)</sup>
	SD	0.078	0.125	0.134
Maximal $\Sigma$ QRS ( $\mu$ V):				
With LVH	mean	2294	2454	1862
	SD	199	212	634
Without LVH	mean	1548	1378	1526
	SD	255	274	239

(x)  $p < 0.01$  between Group I and Group III

## Results and discussion:

The blood pressure values of all men in Groups I - III were compared to data of same subjects measured 7 years before by the same examiner. In the Groups II and III there was a statistically significant elevation of both systolic and diastolic blood pressures (paired t-test  $p < 0.01$ ). Group I was in the same range than 7 years before as well as the 133 men who had got medication for the treatment of hypertension.

The differences in QS2, PEP and PEP/LVET values as well as the differences in maximal spatial vectors in each group is presented in Table I. The STI values are higher in Group I and III than in Group II. The difference between Group I and III is statistically significant. This is in accordance with previous results from the same factory population (6). The maximal spatial vectors did not differ between the groups but there was a good correlation between left ventricular hypertrophy found by visual reading (Minnesota code 3-1 and 3-3) and the spatial QRS vector that was evidently higher in these men. In group I that means men with normal blood pressure was found 8 men with ECG consistent with the criteria of left ventricular hypertrophy. In Group II there was 11 and in Group III 7 men with the same electrocardiographic diagnosis. This means that the visual interpretation or the use of spatial vector do not separate hypertensive patients on the basis of left ventricular hypertrophy from normal people. The QRS and T vectors in the frontal plane were in the normal range among all subjects examined.

The lengthening of the STI values must be interpreted to signify a lengthening of the ventricular activation and pressure generation (4, 5, 6). The heart needs more time to reach the diastolic pressure and to open the aortic valve and this is seen in the

prolongation of PEP These findings are in accordance with experimental and clinical studies but all investigations have not confirmed them (1-7)

Table 1 Systolic time intervals and maximal spatial QRS vectors in the subjects included in the study

		Group I	Group II	Group III
Age		51 $\pm$ 9	48 $\pm$ 8	51 $\pm$ 10
QST index (ms)	mean	494.4	500.7	508.5 <sup>(x)</sup>
	SD	118.1	27.8	32.4
PEP index (ms)	mean	113.1	120.2	130.1 <sup>(x)</sup>
	SD	20.2	31.2	27.7
PEP/LVET	mean	0.328	0.362	0.406 <sup>(x)</sup>
	SD	0.078	0.125	0.134
Maximal E QRS (pV)				
With LVH	mean	2294	2454	1862
	SD	199	212	634
Without LVH	mean	1548	1378	1526
	SD	255	274	239

(x)  $p < 0.01$  between Group I and Group III



## References

- Braunwald E Sarnoff S J & Stainsby W N Determinants of duration and mean rate of ventricular ejection *Circulation Res* 5:319 1958
- Ibrahim M M Tarazi R C Dustan H P & Bravo E L: Cardioadrenergic factor in essential hypertension *Am Heart J* 88:724-732 1974
- Jokinen Y Raunio M Tiihonen J Vehkamäki E & Vilimäki I Design principles of the system for automated ECG analysis in the area of Kuopio University Hospital Data Processing in Electrocardiology ed Kallio V & Viinamäki I Publications of the Social Insurance Institution Finland 1973 pp 83-92
- Jost A G D Systolic time intervals of the cardiac cycle as an index of early cardiac involvement in hypertensive and ischemic heart disease Dalhousie University Halifax Nova Scotia Canada 1976
- Shaver J A Kroetz P W Leonard J J & Paley H W The effect of steady-state increases in systemic arterial pressure on the duration of left ventricular ejection time *J Clin Invest* 47:217 1968
- Takkunen J T Ollinki O I Linnaluoto M M K & Rautaharju P H: Systolic and diastolic intervals of the cardiac cycle in normal men *Annals Clin Res* 9:193-200 1977
- Weissler A M Peeler R G Roehrig W H Jr: Relationships between left ventricular ejection time stroke volume and heart rate in normal individuals and patients with cardiovascular disease *Am Heart J* 62:367 1961
- Wiggers C J Studies on the consecutive phases of the cardiac cycle II The laws governing the relative durations of ventricular systole and diastole *Am J Physiol* 56:439 1921

## HDL-cholesterol in antihypertensive treatment.

### The Oslo Study.

Anders Helgeland Paul Leren Sven Chr Enger

Ingvar Hjermann & Ingar Holme

From Medical Out Patient Clinic, Ullevaal Hospital, Oslo 1

The importance of the cholesterol fraction of the high density lipoprotein (HDL) is a new aspect in the lipid theory of atherogenesis. Recent reports have shown increased coronary risk in subjects with low HDL-cholesterol values (3,6). Antihypertensive drugs have been shown to induce various untoward metabolic changes; increase in serum uric acid (7), triglycerides (1,4) glucose (8) and total cholesterol (1) in thiazide treatment and uric acid increase with beta blockers (2). A triglyceride increase has also been reported in a  $\beta$  1 selective adrenergic blocker (9). Furthermore, beta blockers seem to accentuate the triglyceride and uric acid increasing effect of thiazides (5). As all these metabolic changes may represent increased coronary risk, it seemed reasonable also to study the effect of some antihypertensive drug regimens on the serum concentration of HDL-cholesterol.

785 men age 40-49, with no symptoms of cardiovascular disease and with a systolic blood pressure of 150-179 mm Hg and a diastolic blood pressure below 110 mm Hg were in 1973 randomized for a controlled drug treatment study.

Treatment Hydrochlorothiazide (HCTH) 50 mg daily  
Alpha methyl dopa was added if blood pressure remained above 140/90 In case of side effects, alpha methyl dopa was replaced by propranolol Generally, no advice concerning diet, smoking and weight reduction were given to any group Men with alcohol problems, those having received detailed diet instructions from other physicians and those with cardiovascular events were excluded from the material in this report

In the autumn 1977 HDL-cholesterol was analysed in fresh serum samples at the routine follow-ups The same analysis was performed in non-fasting pretreatment sera stored at - 20°C from 1973 The HDL-cholesterol values in frozen sera were about 39 per cent lower than in fresh sera, and have been used only for selection of comparable groups in the different drug regimens on pretreatment lipid values

The groups were matched on the basis of mean and distribution values of pretreatment HDL-cholesterol The untreated control group (n=33) and the groups treated with HCTH + propranolol (n=33) and HCTH + alpha methyl dopa (n=33) were also well comparable with regard to pretreatment triglycerides The group treated with HCTH alone (n=26) compared well with the others with regard to pretreatment HDL-cholesterol, but tended to have somewhat lower triglycerides

After 4 year treatment the HDL-cholesterol value was 15 per cent lower in the HCTH-propranolol group as compared to the HCTH-methyl dopa group, and 19 and 20 per cent lower than in the HCTH-alone and the untreated control group, respectively

The HCTH + propranolol regimen also induced a distinct triglyceride increase and a more marked uric acid increase than the other drug regimens. Total serum cholesterol did not change significantly in the various treatment groups.

The low HDL-cholesterol level together with the unchanged total cholesterol implies that the sum of low density lipoprotein (LDL) and very low density lipoprotein (VLDL) cholesterol increased during treatment with thiazide combined with propranolol. From a metabolic and epidemiological point of view it is possible that the reported untoward metabolic changes by this frequently used anti-hypertensive drug combination may counteract the beneficial effect of pressure lowering. These observations need to be confirmed in future studies specifically designed for this purpose.

Treatment Hydrochlorothiazide (HCTH) 50 mg daily  
Alpha methyl dopa was added if blood pressure remained above 140/90. In case of side effects, alpha methyl dopa was replaced by propranolol. Generally, no advice concerning diet, smoking and weight reduction were given to any group. Men with alcohol problems, those having received detailed diet instructions from other physicians and those with cardiovascular events were excluded from the material in this report.

In the autumn 1977 HDL-cholesterol was analysed in fresh serum samples at the routine follow-ups. The same analysis was performed in non-fasting pretreatment sera stored at  $-20^{\circ}\text{C}$  from 1973. The HDL-cholesterol values in frozen sera were about 39 per cent lower than in fresh sera, and have been used only for selection of comparable groups in the different drug regimens on pretreatment lipid values.

The groups were matched on the basis of mean and distribution values of pretreatment HDL-cholesterol. The untreated control group ( $n=33$ ) and the groups treated with HCTH + propranolol ( $n=33$ ) and HCTH + alpha methyl dopa ( $n=33$ ) were also well comparable with regard to pretreatment triglycerides. The group treated with HCTH alone ( $n=26$ ) compared well with the others with regard to pretreatment HDL-cholesterol, but tended to have somewhat lower triglycerides.

After 4 year treatment the HDL-cholesterol value was 15 per cent lower in the HCTH-propranolol group as compared to the HCTH methyl dopa group, and 19 and 20 per cent lower than in the HCTH-alone and the untreated control group, respectively.

The HCTH + propranolol regimen also induced a distinct triglyceride increase and a more marked uric acid increase than the other drug regimens. Total serum cholesterol did not change significantly in the various treatment groups.

The low HDL-cholesterol level together with the unchanged total cholesterol implies that the sum of low density lipoprotein (LDL) and very low density lipoprotein (VLDL)-cholesterol increased during treatment with thiazide combined with propranolol. From a metabolic and epidemiological point of view it is possible that the reported untoward metabolic changes by this frequently used anti-hypertensive drug combination may counteract the beneficial effect of pressure lowering. These observations need to be confirmed in future studies specifically designed for this purpose.

## References

- 1 Ames, R P & Hill, P : Elevation of serum lipid levels during diuretic therapy of hypertension  
Am J Med 61 748, 1976
- 2 Anderson, O Berglund, G , Larsson, O et al  
Saluretika eller betablokkerare vid hypertoni-behandling  
Läkartidningen 73 1824, 1976
- 3 Gordon, T , Castelli, W P , Hjortland, M , Kannel, W B & Dawber, T R High density lipoprotein as a protective factor against coronary heart disease The Framingham Study  
Am J Med 62, 707, 1977
- 4 Helgeland, A , Hjermann, I , Holme, I & Leren, P  
Serum triglycerides and serum uric acid in untreated and thiazide-treated patients with mild hypertension  
The Oslo Study  
Am J Med 64, 34, 1978
- 5 Helgeland, A , Hjermann, I , Leren, P & Holme, I  
Possible metabolic side effects of beta-adrenergic blocking drugs  
Brit Med J 1, 828, 1978
- 6 Miller, G J & Miller, N E : Plasma-high-density-lipoprotein concentration and development of ischemic heart disease  
Lancet 1, 16, 1975
- 7 Oren, B, G , Rich, M & Belle, M S Chlorothiazide as hyperuricaemic agent  
JAMA 168, 2128, 1958
- 8 Shapiro, A P , Benedek, Th G & Small, J L :  
Effect of thiazides on carbohydrate metabolism in patients with hypertension  
N Engl J Med 265, 1028, 1961
- 9 Waal-Manning, H J Metabolic effects of beta-adrenoreceptor blockers  
Drugs 11 (suppl 1): 121, 1976

On the pathogenetic role of prostaglandins  
in Bartter's syndrome.

Ingolf Wiel n Birg r He se and Poul Christensen  
From Medical Department B Rigshospitalet and the  
University Institut for Experimental Medicine  
Copenhagen DK-2100 Denmark

Abstract Two patients with Bartter's syndrome and one  
with severe abuse of diuretics were investigated before and  
after indomethacin treatment. Before indomethacin the two  
patients showed a similar pattern of hypokalaemic alkalosis  
secondary hyperaldosteronism and increased urinary excretion  
of  $\text{PGE}_2$  and kallikrein. After a few days on peroral indomethacin  
medication the hypokalaemia was significantly improved  
the plasma renin activity and the urinary excretion of aldosterone.  
 $\text{PGE}_2$  and kallikrein were normalized in both patients.  
It is concluded that the beneficial effect of indomethacin  
cannot be used as a proof of prostaglandin overproduction as  
the primary defect in Bartter's syndrome.

Recently Bartter's syndrome (BS) - a condition of hypokalaemic  
alkalosis hyperaldosteronism hyperplasia of the juxtaglomerular  
apparatus and normal blood pressure without oedema - has  
been associated with overproduction of renal prostaglandins  
and the manifestation of the condition have been successfully  
treated with agents inhibiting prostaglandin synthesis (4,6).  
Consequently it was suggested that prostaglandin overproduction  
was the primary defect in BS.

In 1973 our group presented a report on three cases of BS (9):  
two adults and one child. Since then one of the adults died  
suddenly presumably of cardiac arrhythmia. We found it of interest  
to review the remaining two cases in a protocol with measurement  
of prostaglandin ( $\text{PGE}_2$ ) and kallikrein excretion before and  
after indomethacin treatment.

Material The patients included our original cases 1 and 3 (9).

Case 1 53 year old woman. After the establishment of the diagnosis  
of BS in 1970 she was started on triamterene 25 mg/day  
and potassium supplement 90 mmol/day and advised to take abundant  
salt to her diet. Yet the hypokalaemia was poorly controlled.



(serum potassium concentration =  $1.5 - 3.0$  mmol/l)

Case 3 18 year old woman After the establishment of the diagnosis of BS in 1971 she was started on triamterene 150 mg/day and potassium supplement 45 mmol/day and sodium supplement 80 mmol/day In the subsequent 5 years the patient has grown 12 cm (height now 154 cm) and the body weight has increased by 12 kg

Protocol The patients were started on a metabolic diet with sodium and potassium content approximating their usual diet and they received their usual triamterene dosage (fig 1 phase I) After four days triamterene was discontinued and sodium intake was reduced to normal amounts (120 mmol in case 1 and 70 mmol in case 3) The potassium intake was unchanged (fig 1 phase II) After four days treatment with indomethacin (Confortid<sup>R</sup> Dumex Denmark) was started (case 1: 200 mg/day case 3: 100 mg/day) After 8-10 days of treatment the study was terminated The 24 hour urine production was collected throughout the study and analyzed for sodium potassium and creatinine concentration Excretion of aldosterone  $PGE_2$  and kallikrein was measured Qualitative screening for diuretics was performed on all urine samples In the morning after 60 minutes supine rest blood samples were drawn every day in case 1 and approximately every other day in case 3 Plasma was analysed for sodium and potassium concentrations and renin activity (PRA) Every morning before breakfast the patients were weighed and blood pressure was measured

Methods PRA was measured by radio-immuno assay with the NEN angiotensin I  $^{125}I$  kit normal range  $0.7 - 2.9$  ng/h x ml Aldosterone excretion rate (AER) was measured by radio-immuno assay with the CIS  $^3H$  - aldosterone kit normal range  $8-37$   $\mu g/24h$   $PGE_2$  was measured by the method of Christensen and Leyasac (2) The range of  $PGE_2$  excretion in 6 healthy individuals on liberal salt intake was  $189 - 293$   $\mu g/24 h$  Kallikrein excretion was determined by a combination of the method of Beaven et al (1) and Mac Farlane et al (8) The range of kallikrein excretion in six healthy individuals on liberal salt intake was  $3.5 - 13$  EU/24 h Screening for diuretics (furosemide bumetanide and chlorthalidone) in urine was performed by thin-layer chromatography

## Results (fig 1)

Phase I, triamterene treatment Both patients demonstrated pronounced hypokalaemic alkalosis with very high PRA values. AER was elevated in case 3 and high normal in case 1. Urinary  $\text{PGE}_2$  excretion was elevated in both cases while kallikrein excretion was above control range in case 1 and within the control range in case 3. Plasma sodium concentration was normal in case 3 and slightly lowered in case 1. Blood pressure was low normal in both cases. Creatinine clearance was normal.

Phase II, discontinuation of triamterene, reduction of sodium intake to normal Both cases showed a light weight loss (1 kg). Reduction of AER in case of kallikrein excretion and largely unchanged PRA, plasma sodium and plasma potassium concentrations and  $\text{PGE}_2$  excretion. Blood pressure was unchanged.

Phase III, indomethacin treatment Both cases showed a rapid fall in renal weight (1 and 2 kg respectively). Plasma potassium increased and a plateau was not reached within the study period. PRA, AER, urine  $\text{PGE}_2$  and kallikrein showed a sizeable decrease and reached a plateau in normal range. In both cases a large reduction in sodium excretion was seen in the same period. Plasma sodium concentration was largely unchanged in both cases. Blood pressure was unchanged in both cases.

Screening for diuretics in urine All 24 hour urine collections in case 1 contained furosemide, bumetanide and chlorthalidone. The urine from case 3 was free of diuretics.

Discussion The clinical and laboratory findings in our two patients closely resemble the case of BS earlier described (4, 6, 8). After the demonstration of diuretics in all urine samples from case 1 it can be safely assumed that this patient belongs to the so-called pseudo Bartter syndrome due to covert self-administration of diuretics. It has recently been shown that indomethacin reduces PRA and AER in normal and hypertensive human individual (3, 5) both on normal salt intake and during sodium restriction. The response is associated with transient diuresis and weight increase. Then the action of indomethacin in BS is not unique but coincides with features of secondary hypertension as well. In the light of these two patients it is obvious that the indomethacin effect cannot be used as a proof of prostaglandin overproduction as the primary defect in P

(serum potassium concentration = 1.5 - 3.0 mmol/l)

Case 3 18 year old woman After the establishment of the diagnosis of BS in 1971 she was started on triamterene 150 mg/day and potassium supplement 45 mmol/day and sodium supplement 80 mmol/day In the subsequent 5 years the patient has grown 12 cm (height now 154 cm) and the body weight has increased by 12 kg

Protocol The patients were started on a metabolic diet with sodium and potassium content approximating their usual diet and they received their usual triamterene dosage (fig 1 phase I) After four days triamterene was discontinued and sodium intake was reduced to "normal" amounts (120 mmol in case 1 and 70 mmol in case 3) The potassium intake was unchanged (fig 1 phase II) After four days treatment with indomethacin (Confortid<sup>R</sup> Dumex Denmark) was started (case 1: 200 mg/day case 3: 100 mg/day) After 8-10 days of treatment the study was terminated The 24 hour urine production was collected throughout the study and analyzed for sodium potassium and creatinine concentration Excretion of aldosterone  $PGE_2$  and kallikrein was measured Qualitative screening for diuretics was performed on all urine samples In the morning after 60 minutes supine rest blood samples were drawn every day in case 1 and approximately every other day in case 3 Plasma was analyzed for sodium and potassium concentrations and renin activity (PRA) Every morning before breakfast the patients were weighed and blood pressure was measured

Methods PRA was measured by radio-immuno assay with the NEN angiotensin I  $^{125}I$  kit normal range = 7 - 29 ng/h x ml Aldosterone excretion rate (AER) was measured by radio-immuno assay with the CIS  $^3H$  - aldosterone kit normal range 8-37  $\mu g/24h$   $PGE_2$  was measured by the method of Christensen and Leyssac (2) The range of  $PGE_2$  excretion in 6 healthy individuals on liberal salt intake was 189 - 293  $\mu g/24 h$  Kallikrein excretion was determined by a combination of the method of Beaven et al (1) and MacFarlane et al (8) The range of kallikrein excretion in six healthy individuals on liberal salt intake was 3.5 - 13.8 EU/24 h Screening for diuretics (furosemide bumetanide and chlorthalidone) in urine was performed by thin-layer chromatography

## Result (fig 1)

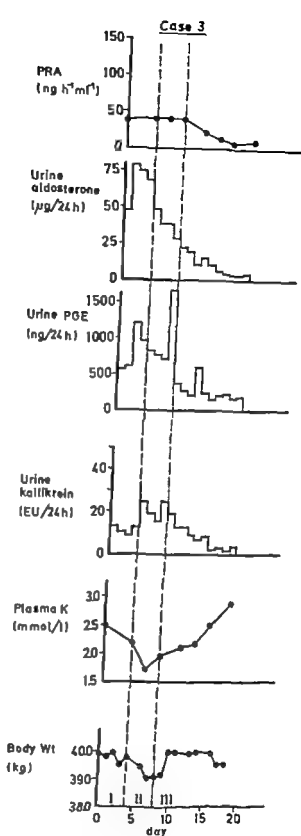
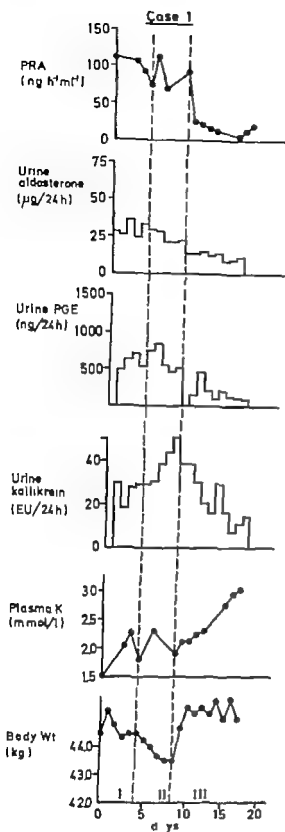
Phase I, triamterene treatment Both patients demonstrated pronounced hypokalaemic alkalosis with very high FRA values. AER was elevated in case 3 and high normal in case 1. Urinary POE excretion was elevated in both cases while kallikrein excretion was above control range in case 1 and within the control range in case 3. Plasma sodium concentration was normal in case 3 and slightly lower in case 1. Blood pressure was low normal in both cases. Creatinine clearance were normal.

Phase II, discontinuation of triamterene, reduction of sodium intake to normal Both cases showed a slight weight loss (1 kg) reduction of AER in case of kallikrein excretion and largely unchanged FRA plasma sodium and plasma potassium concentrations and POE<sub>2</sub> excretion. Blood pressure was unchanged.

Phase III, indomethacin treatment Both cases showed a rapid small increase in weight (1 and 2 kg respectively). Plasma potassium increased and a plateau was not reached within the study period. FRA, AER, urine POE and kallikrein showed a slight decrease and reached a plateau in normal range. In both cases a large reduction in sodium excretion was seen in the same period. Plasma sodium concentration was largely unchanged in both cases. Blood pressure was unchanged in both cases.

Summary of diuretics in urine All 24 hour urine collection in case 1 contained furosemide, bumetanide and chlorthalidone. The urine from case 3 was free of diuretics.

Discussion The clinical and laboratory findings in our two patients closely resemble the cases of BS earlier described (4, 5, 8). After the demonstration of diuretics in all urine samples from case 1 it can be safely assumed that the patient belongs to the so-called pseudo-Bartter syndrome due to covert self-administration of diuretics. It has recently been shown that indomethacin reduces FRA and AER in normal and hypertensive human individual (3, 3) both on normal salt intake and during sodium restriction. The response is associated with transient diuresis and weight increase. Thus the action of indomethacin in BS is not unique but seen in states of secondary hyperaldosteronism as well. In the light of the two patients it is obvious that the indomethacin effect cannot be used as a proof of prostaglandin overproduction as the primary defect in BS



Legend to Fig. 1

Plasma renin activity (PRA) plasma potassium concentration body weight and urinary excretion of aldosterone  $\text{PGE}_2$  and kallikrein in the three phases of the investigation I treatment with triamterene High sodium intake II triamterene alone III alone Normal sodium intake III indomethacin treatment Normal sodium intake

## References

- 1 Beaven V H Pierce J V and Pisano J J (1971) A sensitive isotopic procedure for the assay of esterase activity: Measurement of human urinary kallikrein  
Clinica Chimica Acta 32 67-73
- 2 Christensen P and Leyssac P P (1976) A specific radioimmunoassay for  $\text{PGE}_2$  using an antibody with high specificity and a sephadex LH-20 microcolumn for the separation of prostaglandins  
Prostaglandins 11 399-420
- 3 Donker A J M Arisz L Brentjens J R H van der Hem G F and Hollemans H J G (1976) The effect of indomethacin on kidney function and plasma renin activity in man  
Nephron 17 288-296
- 4 Fichman M F Telfer H Xia P Speckart P Golub M and Rude R (1976) Role of prostaglandins in the pathogenesis of Bartter's syndrome  
The American Journal of Medicine 60 785-797
- 5 Frölich J C Hollifield J W Dormois J C Frölich B L Seyberth H Michelakis A H and Oates J A (1976) Suppression of plasma renin activity by indomethacin in man  
Circulation Research 39 447-452
- 6 Gill J R Frölich J C Bowden R E Taylor A A Feiser H R Seyberth H W Oates J A and Bartter F C (1976) Bartter syndrome A disorder characterized by high urinary prostaglandins and a dependence of hyperreninemia on prostaglandin synthesis  
The American Journal of Medicine 61 43-51

- 7 Lechi A Govi G Lechi, C Mantero F and Scuro, L A  
(1976) Urinary kallikrein excretion in Bartter's syndrome  
Journal of Clinical Endocrinology and Metabolism  
43 1175-1178
- 8 Mills J H and Ward, P E (1975) The relationship between  
kallikrein and water excretion and the conditional relation-  
ship between kallikrein and sodium excretion  
Journal of Physiology 246 695-707
- 9 Nielsen I Jacobsen J G and Olesen K H (1973)  
On the pathogenesis of the secondary hyperaldosteronism of  
the Bartter syndrome  
Clinical Science and Molecular Medicine 45 301-304

TREATMENT OF HYPERTENSION WITH PRazosin. AN OPEN STUDY IN GENERAL PRACTICE.

Per Fauchald M.D. and Anders Helgeland M.D.  
Hedmark Sentralsjukhus 2400 Elverum and Medical Out-Patient Clinic  
Ullevaal Hospital Oslo 1

In a field trial 147 general practitioners provided case reports on 1151 patients with essential hypertension treated in twelve weeks with prazosin. The main purpose of the study was to evaluate the frequency of side-effects and especially the frequency of the initial reaction reported after the first dose of prazosin(1). Blood pressure, pulse rate and side-effects were registered before treatment with prazosin and after 4, 8 and 12 weeks. For the first four weeks prazosin was given in a fixed dose with 0.5 mg in the evening for the first two days, 0.5 mg b.i.d. for the rest of the first week, 1 mg b.i.d. in the second week and thereafter 2 mg b.i.d. After the control at four weeks the dose was adjusted individually with a maximum dose of 5 mg b.i.d.

Of the 1151 patients there was 51% female and 49% male, the mean age was 59.4 years. Prazosin was given as the sole antihypertensive agent in 533 patients, 246 patients were treated with prazosin and a diuretic, 162 with prazosin and a beta-blocking agent and 210 with prazosin in other combinations. At the twelve weeks control the mean dose of prazosin was 4.9 mg/day in the group treated with prazosin alone and from 4.8 to 5.7 mg/day in the various groups treated with prazosin in combination with other antihypertensive agents. Side-effects were mild and mostly of short duration. The treatment with prazosin was discontinued in 9.5% of the patients because of side-effects and/or unsatisfactory effect on the blood-pressure. Dizziness, often of postural type was the most common side-effect (table 1). No case of typical first dose phenomenon was noted. Later in the twelve week periods 7 patients (0.6%) had short-lasting



- 7 Lechi, A Govi, G Lechi C Mantero F and Scuro L A  
(1976) Urinary kallikrein excretion in Bartter's syndrome  
Journal of Clinical Endocrinology and Metabolism  
43 1175-1178
- 8 Mills J H and Ward P E (1975) The relationship between  
kallikrein and water excretion and the conditional relation-  
ship between kallikrein and sodium excretion  
Journal of Physiology 246 695-707
- 9 Nielsen I Jacobsen J Ø and Olesen K H (1973)  
On the pathogenesis of the secondary hyperaldosteronism of  
the Bartter syndrome  
Clinical Science and Molecular Medicine 45 301-304

TREATMENT OF HYPERTENSION WITH PRAZOSIN. AN OPEN STUDY IN GENERAL PRACTICE.

Per Fauchald M.D. and Anders Halgeland M.D.  
Hedmark Sentralsjukhus 2400 Elverum and Medical Out-Patient Clinic  
Ullevaal Hospital Oslo 1

In a field trial 147 general practitioners provided case reports on 1151 patients with essential hypertension treated in twelve weeks with prazosin. The main purpose of the study was to evaluate the frequency of side-effects and especially the frequency of the initial reaction reported after the first dose of prazosin(1)

Blood pressure pulse rate and side-effects were registered before treatment with prazosin and after 4,8 and 12 weeks. For the first four weeks prazosin was given in a fixed dose with 0,5 mg in the evening for the first two days, 0,5 mg b i d for the rest of the first week 1 mg b i d in the second week and thereafter 2 mg b i d. After the control at four weeks the dose was adjusted individually with a maximum dose of 5 mg b i d.

Of the 1151 patients there was 51% female and 49% male, the mean age was 59,4 years. Prazosin was given as the sole antihypertensive agent in 533 patients, 246 patients were treated with prazosin and a diuretic, 162 with prazosin and a beta-blocking agent and 210 with prazosin in other combinations. At the twelve weeks control the mean dose of prazosin was 4,9 mg /day in the group treated with prazosin alone and from 4,8 to 5,7 mg /day in the various groups treated with prazosin in combination with other antihypertensive agents. Side-effects were mild and mostly of short duration. The treatment with prazosin was discontinued in 9,5% of the patients because of side-effects and/or unsatisfactory effect on the blood-pressure. Dizziness, often of postural type, was the most common side-effect (table 1). No case of typical first dose phenomenon was noted. Later in the twelve week periode 7 patients (0,6%) had short-lasting

syncope. No other serious side-effects were noted

In the group of previously untreated patients prazosin as a sole agent gave a fall in blood-pressure of 14% systolic and 13% diastolic. In combination with a diuretic or a betablocker we noted an additive blood-pressure reducing effect.

It is concluded that with the low starting dose used in this study the first-dose phenomenon was not seen, and that side-effects noted were mostly subjective side-effects which are common in the first phase of all antihypertensive treatment.

	4 weeks	8 weeks	12 weeks
Dizziness	14,9	6,4	4,2
Fatigue	9,8	5,2	2,8
Palpitations	6,0	2,2	1,9
Headache	3,9	1,9	0,9
Nausea	3,5	1,3	0,6
Syncope	0,35	0,18	0,09
Other side-effects	9,3	5,0	3,9

Table 1 Percentage of patients on treatment with side-effects

### References

- 1 Brogden R.N., Heel R.C., Speight T.M. and Avery G.E.: Prazosin: A Review of its Pharmacological Properties and Therapeutic Efficacy in Hypertension. *Drugs* 14, 163-197, 1977





# Acta Medica Scandinavica

Supplementum 626

## Hypertension Control in Scandinavia

*Proceedings of a Dumex symposium held in Copenhagen  
November 4th-5th, 1977*

Edited by Bent Harvald and Kjeld Rytting

# Acta Medica Scandinavica

originally published as *Nordiskt Medicinskt Arkiv* was founded in 1869 by professor Axel Key MD In 1901 (from volume 34) this journal was divided into a medical and a surgical section Since 1919 (from volume 52) the medical section has been published under the name of *Acta Medica Scandinavica*.

## *Acta Medica Scandinavica*

publishes papers on general medicine mainly from Denmark Finland Iceland Norway Sweden and the Netherlands Short preliminary reports (not exceeding two pages) will be published at short notice The papers are published in English French or German *Acta Medica Scandinavica* is published on a non profit basis

## *Subscriptions*

to *Acta Medica Scandinavica* (two volumes of six numbers each annually) include free supplements to the current volumes

## *Subscription Rates*

Per annum = two volumes

In Denmark Finland Iceland Norway Sweden and the Netherlands Sw cr 330 incl postage

Other countries Sw cr 375 incl postage

## *Chief Editor*

Professor Jan G Waldenström MD  
*Acta Medica Scandinavica*  
Kungsgatan 54  
S-111 35 Stockholm, Sweden

## *Editorial Office*

*Acta Medica Scandinavica*  
Kungsgatan 54  
S-111 35 Stockholm Sweden  
(All correspondence concerning manuscripts and editorial matters)  
Telephone 08/21 77 63

## *Subscription Distribution and Advertising*

The Almqvist & Wiksell Periodical Company  
Gamla Brogatan 26 Box 62  
S-101 20 Stockholm 1 Sweden

## *Printers*

Almqvist & Wiksell Tryckeri AB  
S-751 81 Uppsala, Sweden

# Acta Medica Scandinavica

Supplementum 828

## Hypertension Control in Scandinavia

*Proceedings of a Dumex symposium held in Copenhagen  
November 4th 5th 1977*

Edited by Bent Harvald and Kjeld Rytting



# Acta Medica Scandinavica

originally published as *Nordiskt Medicinskt Arkiv* was founded in 1869 by professor Axel Key MD. In 1901 (from volume 34) this journal was divided into a medical and a surgical section. Since 1919 (from volume 52) the medical section has been published under the name of *Acta Medica Scandinavica*.

## *Acta Medica Scandinavica*

publishes papers on general medicine mainly from Denmark, Finland, Iceland, Norway, Sweden and the Netherlands. Short preliminary reports (not exceeding two pages) will be published at short notice. The papers are published in English, French or German. *Acta Medica Scandinavica* is published on a non-profit basis.

## *Subscriptions*

to *Acta Medica Scandinavica* (two volumes of six numbers each annually) include free supplements to the current volumes.

## *Subscription Rates*

Per annum = two volumes

In Denmark, Finland, Iceland, Norway, Sweden and the Netherlands Sw. cr. 330 incl. postage.

Other countries Sw. cr. 375 incl. postage.

## *Chief Editor*

Professor Jan G. Waldenström MD  
*Acta Medica Scandinavica*  
Kungsgatan 54  
S-111 35 Stockholm, Sweden

## *Editorial Office*

*Acta Medica Scandinavica*  
Kungsgatan 54  
S-111 35 Stockholm, Sweden  
(All correspondence concerning manuscripts and editorial matters)  
Telephone 08/21 77 63

## *Subscription, Distribution and Advertising*

The Almqvist & Wiksell Periodical Company  
Gamla Brogatan 26, Box 62  
S-101 20 Stockholm 1, Sweden

## *Printers*

Almqvist & Wiksell Tryckeri AB  
S-751 81 Uppsala, Sweden

# Participants

## *Denmark:*

Agner, Erik, København  
 Appleyard, Merete, København  
 Beckgaard, Povl, Århus  
 Bjerregaard, Vibeke, København  
 Boye, Ernst, Århus  
 Buch, Nanna, København  
 Dawling, Martin, Frederiksberg  
 Eclsa, Tage, København  
 Elkjær, Jørgen, København  
 Ehngræn, Jens, Glostrup  
 Enksen, Marie, Ørre Strand  
 Gæst, Jera, Glostrup  
 Gynæborg, Elza, København  
 Hagerup, L., Holstebro  
 Hansen, Anders Tybjerg, København  
 Hansen, Tage, København  
 Harvald, Bent, Odense  
 Haselag, Jette, København  
 Hildea, Tage, Frederiksberg  
 Høbbeel, Hanne, Glostrup  
 Holm-Madsen, Niels, København  
 Høfter Kristna, København  
 Høy Elisebeth, København  
 Isen, Hans, Glostrup  
 Jensen, Gorm, København  
 Jensen, H. Ærendsen, Hvidovre  
 Kristrup, Lis, København  
 Kriegerholm, Birgitte, Frederiksberg  
 Kruschken, Bodo, København  
 Kroppgaard, Arne R., Frederiksberg  
 Lærdsen, Lone, Roskilde  
 Løtzi, Jytte, København  
 Løvi, Arne, Glostrup  
 Mabeck, Carl Erik, København  
 Madsen, E. Burk, Glostrup  
 Møllinggaard, Kresten, Hølsed  
 Nielsen, Povl Ebbe, Frederiksberg  
 Pedersen, Ole Lederballe, Århus  
 Petersen, V. Poulsen, Århus  
 Rasmussen, Søren, Frederiksberg  
 Rytting, Kjeld, København  
 Schaefer Peter, København  
 Schrøf, Mariusne, København  
 Sørensen, Tage Lybjo, Frederiksberg  
 Trap-Jensen, Jens, Frederiksberg  
 Videbæk, Jørgen, Århus  
 Whit, Karl, Frederiksberg  
 Aarve, Ingvald, København

## *Finland:*

Elmlo, Antti, Helsinki  
 Kallio, Mikko, Pori  
 Kobvalke, Antti, Helsinki  
 Niskanen, Aulikki, Kuopio  
 Panka, Pekka, Kuopio  
 Ruos, Anders, Helsinki  
 Tuomelahto Jaakko, Kuopio  
 Tötterman, K. J. Helsinki

## *Iceland:*

Kristjánsson, Arni, Reykjavík  
 Smorrsson, Sæmri P. Reykjavík

## *Norway:*

Berg, Knut Jonsson, Trondheim  
 Bjartveit, Kjell, Oslo  
 Enger, Erik, Oslo  
 Helgehaug, Anders, Oslo  
 Holte, Martin, Trondheim  
 Hinnerfeldt, Sigurd, Bergen  
 Loren, Paul, Oslo  
 Lund-Johansen, Per, Bergen  
 Lund-Larsen, Per G., Oslo  
 Myhre, Erik, Oslo  
 Sembræk, Ørulf, Lillehammer  
 Storm-Mathisen, Haakon, Oslo  
 Thelle, Dag, Tromsø  
 Waaler, Hans Th., Oslo  
 Westly Torvald, Høvik  
 Ånstad, Unni, Tromsø

## *Sweden:*

Berglund, Göran, Göteborg  
 Cullhed, L., Uppsala  
 Fagerberg, Sven-Erik, Örebro  
 Forsberg, Sven Åke, Borås  
 Linnell, Helge, Umeå  
 Olsson, Ole, Malmö  
 Waldenström, Jan, Malmö  
 Wodet, Hans, Göteborg  
 Wiberg, B., Helsingborg  
 Wilhelmsen, Lars, Göteborg



# Contents

Opening address <i>Bent Hørreld</i>	7
The Value of Mass Screening for Hypertension <i>Peter Schnohr</i>	9
The Tromsø Heart Study: The Consequences of Blood Pressure Screening in Men Aged 20-49 Years <i>Dag S. Thelle and Olav H. Førde</i>	13
Threshold Values of Blood Pressure Based upon Mortality and Expected Effects of Treatment <i>Hans Th. Wessler</i>	17
Screening for Hypertension in 5,249 Copenhagen males <i>Finn Gyntelberg and Lone Lauridsen</i>	19
Principles and Experiences of a Community Control Programme for Hypertension, as Part of the North Karelia Project <i>P. Puska, J. Tuomilehto, A. Nissinen, and J. Salonen</i>	22
Epidemiology and Treatment of Hypertension in North Karelia with Special Reference to Detection for Hypertension <i>Jaakko Tuomilehto, Pekka Puska, Aulikki Nissinen, and Jarmo Virtamo</i>	23
Follow-up of the Hypertensive Patients in North Karelia and some Results from the Hypertension Register <i>Aulikki Nissinen, Jaakko Tuomilehto, and Pekka Puska</i>	29
Coronary Risk and Socio-economic Status, the Oslo Study <i>P. Leren, A. Heigeland, I. Hjermann, I. Holme, and P.G. Lund-Larsen</i>	33
Mild Hypertension: Early Drug Treatment or Follow-up only? <i>A. Heigeland, I. Bjerkas Aasen, and P. Leren</i>	34
Prevalence of Hypertension in the Glostrup Population Studies <i>Lef Hegerup, Marianne Schroll, Marie Eriksen, Hanne Holtnagel, and Erik Agner</i>	37
Cardiovascular Manifestations and Changes in Blood Pressure from the Age of 50 to the Age of 60 in the Glostrup Population of Men and Women, Born in 1914 <i>Marianne Schroll</i>	39
The Prevalence of High Blood Pressure among 40 Year Old Men and Women <i>Hanne Holtnagel, Arne Leth, Hans Ibsen, and Finn Kamper Jørgensen</i>	42
Cost of Care of the Hypertensive in the Primary Preventive Trial, Gothenburg <i>Lars Wilhelmsen, Göran Berglund, and Hans Wedel</i>	44
Expenses Concerning Evaluation and Treatment of Hypertension <i>Birgitta Kringsholm and Tage Hilden</i>	47
Standardized Investigation Programme in Patients with Hypertension - a Cost Analysis <i>Sven Åke Forsberg</i>	51
Arterial Hypertension, Examination, Treatment and Nursing Processes in Primary Health Sector and Hospital <i>Niels Holm-Nielsen, Mogens Kjærgård Hansen, and Henning Poulsen</i>	54



# Contents

Opening address <i>Bent Hørrild</i>	7
The Value of Mass Screening for Hypertension <i>Peter Schnohr</i>	9
The Tromsø Heart Study: The Consequences of Blood Pressure Screening in Men Aged 20-49 Years <i>Dag S. Thelle and Olav H. Forder</i>	13
Threshold Values of Blood Pressure Based upon Mortality and Expected Effects of Treatment <i>Hans TA. Wessler</i>	17
Screening for Hypertension in 5,249 Copenhagen males <i>Flur Gyntherberg and Lone Lauridsen</i>	19
Principles and Experiences of a Community Control Programme for Hypertension, as Part of the North Karelia Project <i>P. Puska, J. Tuomilehto, A. Nissinen, and J. Salonen</i>	22
Epidemiology and Treatment of Hypertension in North Karelia with Special Reference to Detection for Hypertension <i>Jaukko Tuomilehto, Pekka Puska, Aulikki Nissinen, and Jarmo Virtamo</i>	25
Follow-up of the Hypertensive Patients in North Karelia and some Results from the Hypertension Register <i>Aulikki Nissinen, Jaukko Tuomilehto, and Pekka Puska</i>	29
Coronary Risk and Socio-economic Status, the Oslo Study <i>P. Leren, A. Helgeland, L. Hjermann, I. Holme and P. G. Lund-Larsen</i>	33
Mild Hypertension: Early Drug Treatment or Follow-up only? <i>A. Helgeland, I. Baksaas Aasen, and P. Leren</i>	34
Prevalence of Hypertension in the Glostrup Population Studies <i>Lelf Hegerup, Marianne Schroll, Marie Eriksen, Hanne Holtnagel, and Erik Agner</i>	37
Cardiovascular Manifestations and Changes in Blood Pressure from the Age of 50 to the Age of 60 in the Glostrup Population of Men and Women, Born in 1914 <i>Marianne Schroll</i>	39
The Prevalence of High Blood Pressure among 40 Year Old Men and Women <i>Hanne Holtnagel, Arne Leth, Hans Rosen, and Flur Kemper-Jørgensen</i>	42
Cost of Care of the Hypertensive in the Primary Preventive Trial: Gothenburg <i>Lars Wilhelmsen, Göran Berglund, and Hans Wedel</i>	44
Expenses Concerning Evaluation and Treatment of Hypertension <i>Birgitte Krægholm and Torge Hilden</i>	47
Standardized Investigation Programme in Patients with Hypertension: a Cost Analysis <i>Sven Åke Forsberg</i>	51
Arterial Hypertension; Examination, Treatment and Nursing Processes in Primary Health Sector and Hospital <i>Arlis Holm-Nielsen, Mogens Kjærgård Hansen, and Henning Poulsen</i>	54



## Opening Address

During these 20 years problems concerning arterial hypertension have totally changed. Effective treatment is now nearly always possible and for severe cases prognosis has radically improved. For patients who start treatment before brain, heart, or kidneys have been damaged, life-expectancy can now be considered normal or nearly normal.

Therapeutic advances have broadened the gap between negligent treatment or no treatment at all on one side and treatment according to current principles on the other. Therapeutic neglect must be considered a professional fault. It has become an obligation for the health system to ensure that society as a whole profits from the therapeutic achievements. The primary purpose is to avoid or delay complications such as stroke, myocardial infarction, or uremia. This can be achieved only by early diagnosis, qualified treatment, careful check-ups, and high patient and therapist compliance.

Related problems have been known for many years with regard to juvenile diabetes. Juvenile diabetes, however, affects less than one per cent of the population. Hypertension demanding treatment affects more than 10 per cent. Juvenile diabetes generally makes itself known by characteristic symptoms, whereas early hypertension is often silent. The diagnosis of juvenile diabetes is generally clear-cut, whereas many cases of hypertension necessitate further elucidation

before treatment. Average costs of treatment of juvenile diabetes are significantly lower than those of antihypertensive therapy. In diabetes both immediate and long-term benefits of treatment are more easily registrable and more comprehensible than in hypertension, where patients often feel worse after starting treatment, and where increased life-expectancy is a question of statistics.

Because of high prevalence hypertension is a major challenge to the health system. Ideal screening, diagnosis, treatment, and maintenance in this single disorder would require 5-10 per cent of today's financial contribution to the entire health sector. This underlines the essential socio-medical aspects of hypertension, which have been made the subject of this symposium.

Today it is not possible to decide which organization should be preferred to obtain ideal service at reasonable costs. The approach has been different in the Scandinavian countries, and has also differed from one center to another. Thus a considerable amount of experience has accumulated, which, however, on no earlier occasion has been presented in a collected form. It is the hope of the organizers that by offering an opportunity to exchange ideas this symposium will inspire further efforts for the benefit of the individual patients and society as a whole.

*Bent Harvold*



How to avoid Inappropriate Antihypertensive Treatment <i>A. Eisafo and K. J. Tötterman</i>	56
The Social and Psychological Consequences of being Long term Treated for Moderate and Severe Hypertension <i>Martin Døssing, Lis Kelstrup, and Tage Hilden</i>	58
Programmed Medical Care in Hypertension Concepts and Ideas <i>Sven Åke Forsberg</i>	61
The Skaraborg Project A Controlled Trial Regarding the Effect of Structured Hypertension Care <i>Göran Berghund, Sven-Olaf Isacson, and Lars Rydén</i>	64
Drug of First Choice in Mild and Moderate Essential Hypertension Clinical Hemodynamic and Economic Aspects <i>Per Lund-Johansen</i>	69
The Organisation of Treatment of Hypertension, the Role of the General Practitioner <i>Sigurd Humerfelt</i>	73
Doctor Patient Relationship in Long-term Treatment of Hypertension <i>H. Storm-Mathisen and K. Heibnes</i>	75

## Opening Address

During these 20 years problems concerning arterial hypertension have totally changed. Effective treatment is now nearly always possible and for severe cases prognosis has radically improved. For patients who start treatment before brain, heart, or kidneys have been damaged life-expectancy can now be considered normal or nearly normal.

Therapeutic advances have broadened the gap between negligent treatment or no treatment at all on one side and treatment according to current principles on the other. Therapeutic neglect must be considered a professional fault. It has become an obligation for the health system to ensure that society as a whole profits from the therapeutic achievements. The primary purpose is to avoid or delay complications such as stroke, myocardial infarction or uremia. This can be achieved only by early diagnosis, qualified treatment, careful check-ups, and high patient and therapist compliance.

Related problems have been known for many years with regard to juvenile diabetes. Juvenile diabetes, however, affects less than one per cent of the population, hypertension demanding treatment affects more than 10 per cent. Juvenile diabetes generally makes itself known by characteristic symptoms, whereas early hypertension is often silent. The diagnosis of juvenile diabetes is generally clear-cut, whereas many cases of hypertension necessitate further elucidation

before treatment. Average costs of treatment of juvenile diabetes are significantly lower than those of antihypertensive therapy in diabetes both immediate and long term benefits of treatment are more easily registrable and more comprehensible than in hypertension, where patients often feel worse after starting treatment, and where increased life-expectancy is a question of statistics.

Because of high prevalence hypertension is a major challenge to the health system. Ideal screening, diagnosis, treatment, and maintenance in this single disorder would require 5-10 per cent of today's financial contribution to the entire health sector. This underlines the essential socio-medical aspects of hypertension, which have been made the subject of this symposium.

Today it is not possible to decide which organization should be preferred to obtain ideal service at reasonable costs. The approach has been different in the Scandinavian countries, and has also differed from one center to another. Thus a considerable amount of experience has accumulated, which, however, on no earlier occasion has been presented in a collected form. It is the hope of the organizers that by offering an opportunity to exchange ideas this symposium will inspire further efforts for the benefit of the individual patients and society as a whole.

*Bent Herreid*



# The Value of Mass Screening for Hypertension

PETER SCHNOHR

From the Department of Medicine B, Rigshospitalet, Copenhagen, Denmark

In a population study the Amager women study 210 randomly selected Copenhagen females aged 25-65 years were examined (10). The data collection was carried out in 1973 and the response rate was 85 per cent. Blood pressure measurements were included in the study. The systolic as well as the diastolic blood pressure rose with age. Within the five age groups, 25, 35, 45, 55 and 65 respectively 7, 16, 42, 56 and 81 per cent had a blood pressure  $\geq 160$  mmHg systolic and/or  $\geq 95$  mmHg diastolic, the W.H.O. criteria for hypertension. Of these 82 women, 24 (29 per cent) knew they had high blood pressure and out of these 11 (46 per cent) received antihypertensive treatment. Three women with values below the W.H.O. criteria received antihypertensive treatment, so altogether 14 (7 per cent) of these 210 women received antihypertensive treatment.

We talk about the half of a half of a half rule (9), which we use to describe the following situation: Only half the hypertensives living in a population are aware of their condition; of these, only half are currently under treatment; and of the individuals currently under treatment, only half are receiving treatment that will adequately reduce the blood pressure levels to acceptable values. Thus only one-eighth of all hypertensives in the community have their blood pressure adequately reduced.

The findings from the Amager women study showed that only one-third of the hypertensives knew of their condition, that half of these were under treatment and that only one-fifth of these were adequately treated. Admittedly the W.H.O. criteria for hypertension are not generally agreed on as a level for medical treatment, but this study shows that a great number of hypertensives are unaware of their condition and

that a high number of the treated patients are not treated adequately.

So the major problems in controlling high blood pressure are getting the symptom-free as well as hypertensives with symptoms to accept medical care, and motivating them for lifelong follow-up and probably life-long treatment.

To meet this challenge more information should be given to the public about the importance of regular blood pressure measurement and more should be done to stimulate the doctors' interest in the follow-up and treatment of hypertension.

Mainly to fulfill these two purposes The Danish Heart Foundation organized a blood pressure screening campaign in supermarkets in February 1975 (11). On five consecutive afternoons some 90 medical students measured the blood pressures of 24,577 persons, 13,747 women and 10,630 men. Each person measured received a card with the BP value and an easy-to-read pamphlet about high blood pressure. Six per cent were aged 19 or less, 26% were 20-39, 43% were 40-59 and 25% were 60 years of age or more. The percentage of women and men correspond well to the total sex distribution in Copenhagen in contrast to the distribution of patients seen in general practice, where women are over-represented.

If the systolic BP exceeded the persons age + 110 (and this sum exceeded 145) and/or the diastolic BP exceeded 100 mmHg for all ages the persons measured were advised to contact their general practitioner for further evaluation. Altogether 3,653 (23%) persons were referred to their general practitioners. 3.7% had systolic values  $\geq 200$ , 1.1%  $\geq 220$  and 0.7%  $\geq 230$ .

Fig. 1 shows median values for systolic and diastolic BP for men and women. The



broudersegehen or the Copenhagen City Heart Study (12). The study population is a random sample of 20,000 men and women. By the end of August 1976, approximately 3,200 had been examined and the initial response rate was 69%.

Fig. 2 shows the median values for men and women and is unique because it is the first time to my knowledge that it has been found that through the entire lifespan women have lower blood pressures than men. The explanation could be that women use more antihypertensive drugs than men and at all ages visit their doctors more frequently than men. Is the latter the reason why women live longer than men?

To conclude: The major problems in controlling high blood pressure are extremely common condition which often goes undetected, untreated or inadequately treated are to get the symptom-free as well as the hypertensives with symptoms to accept medical care and to motivate them for lifelong follow-up and probably lifelong treatment.

To reach this goal we have to begin blood pressure measurement in the schools the only place passed by all persons of the community. We should stress that all doctors should include blood-pressure measurement as a routine. We should now and then perform blood-pressure screenings mainly to inform the public of the importance of the measurements, but also to detect hypertensives who would not otherwise be found. The screening should be undertaken where people are i.e. in supermarkets, at the voting polls, etc.

And finally we should have on-going prospective randomized population studies not only to describe the changes in morbidity and mortality of cardiovascular diseases, but also to serve as bases for further research. I do hope that instead of controlling hypertension only with drugs we shall also be able to control it through other ways such as weight reduction, salt restriction and more physical exercise.

## References

1. Acheson, R.M.: Blood pressure in a national sample of U.S. adults: percentile distribution by age, sex and race. *Int. J. Epidemiol.* 2:293 1973
2. Backer P., Kasper Jørgensen, F., Krugstrup, J. & Pedersen, P.A.: The effect of the Danish Heart Society's blood-pressure campaign in 1975 as seen from general practice. *Ugeskr. Læg.* 138:493 1976.
3. Rea, J., Hamerfeld, S. & Wadervang, F.: The blood pressure in a population. *Acta med. scand., suppl.* 321 1957
4. Carlson, L.A. & Lindstedt, S.: The Stockholm prospective study I. *Acta med. scand., Suppl.* 493 1968.
5. Hart, J.T.: Semiconscious screening of a whole community for hypertension. *Lancet* 2: 223 1970.
6. Johnson, B.C., Epstein, F.H. & Kjelsberg, M.O.: Distributions and familial studies of blood pressure and serum cholesterol levels in total community Tecumseh, Michigan. *J. chron. Dis.* 18 147 1965
7. Karned, W.B., Gordon, T. & Schwartz, M.J.: Systolic versus diastolic blood pressure and risk of coronary heart disease. *Amer. J. Cardiol.* 27 315 1971
8. Lew, E.A.: High blood pressure, other risk factors and longevity: The insurance viewpoint. *Amer. J. Med.* 55 281 1973
9. Remington, R.D.: Control of pressure mortality and morbidity by intervention on elevated blood pressure. The U.S. experience. In: Ischaemic heart disease. The strategy of postponement (Eds. A. Tytjærsg Høsten, P. Schnohr & O. Rose) p. 64 F.A.D.L., Publishing Company Copenhagen 1977
10. Schnohr, P.: Blood pressure in Copenhagen women 25-65 years of age. The Amager women study 1973. *Ugeskr. Læg.* 138, 192, 1976.
11. Schnohr, P. & Hansen, A.T.: A blood pressure information campaign including mass screening for hypertension in Copenhagen supermarkets. *Acta med. scand.* 199- 269 1976.
12. Schnohr, P., Jensen, G., Nyboe, J. & Hansen A.T.: The Copenhagen city heart study. A prospective cardiovascular population study of 20,000 men and women. *Ugeskr. Læg.* 139: 1921 1977
13. Wilhelmsen, L., Berglund, G. & Werkö, L.: Prevalence and management of hypertension in a general population sample of Swedish men. *Prev. Med.* 2: 57 1973

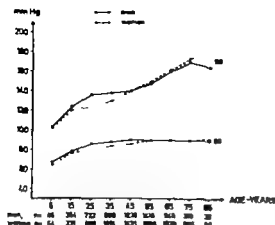


Fig. 1 Systolic and diastolic BP (right arm) in 13 704 men and women (median values) The supermarket campaign 1975

systolic pressure increases almost linearly with age being higher in men than in women until the forties after which age the relation becomes reverse a finding that is in agreement with the general trend in industrialized countries (1 3 4 5 6 7 8 13)

The cost of this screening including salary to the students (US\$ 7 per hour) transportation pamphlets cards and other materials, was US\$ 12,000 or US\$ 0.49 per measurement. Of this amount US\$ 0.11 were for the BP pamphlet.

In order to assess the effect of the campaign the number of patients visiting general practitioners during the week of the campaign and the succeeding week were registered and compared with the corresponding number during a control week six months later (2). Forty-eight practitioners participated in the campaign period and 24 in the control week also. All requests for blood-pressure measurements were included, but patients in current control were excluded. Sixty per cent of the persons referred from the supermarkets had pressures that were still above our values for referral. Twenty-three per cent of those referred had values that are generally accepted as requiring treatment. These values are as follows: for persons under 40 years of age a diastolic pressure above 100 mmHg for 40-49 a value above 105 for 50-59 a value above 110 and for persons 60

and over a value above 115 mmHg. This means that approximately 5% of the persons screened in the supermarkets at their second blood pressure measurement had values requiring treatment. The investigation further showed that there were 2.3 times as many visits to practitioners for measurement of blood pressure in the campaign period as in the control week and the practitioners interest in blood pressure measurements was also greater during the campaign than during the control week six months later indicating that the effect declines with time. On the other hand the use of antihypertensive drugs increased significantly in Denmark the year following the campaign compared to the year before. The total drug consumption has been almost stable in Denmark during the last 10 years.

We felt that the main purposes of the supermarket screening, namely information about a common and health-threatening condition and finding persons with raised blood pressure were achieved. It must be stated that the campaign would not have had the same response without the help of news media. Almost every Dane heard or read about BP during this particular week in February 1975.

In February 1976 we began a prospective cardiovascular population study Øster

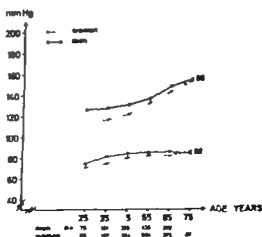


Fig. 2 Systolic and diastolic BP in 3 156 men and women (median values) The Copenhagen City Heart Study 1976

bromoderogehen or the Copenhagen City Heart Study (12). The study population is a random sample of 20 000 men and women. By the end of August 1976, approximately 3,200 had been examined and the initial response rate was 69%.

Fig. 2 shows the median values for men and women and is unique because it is the first time to my knowledge that it has been found that through the entire lifespan women have lower blood pressures than men. The explanation could be that women use more antihypertensive drugs than men and at all ages visit their doctors more frequently than men. Is the latter the reason why women live longer than men?

To conclude: The major problems in controlling high blood pressure are extremely common condition which often goes undetected, untreated or inadequately treated are to get the symptom-free as well as the hypertensives with symptoms to accept medical care and to motivate them for lifelong follow-up and probably life long treatment.

To reach this goal we have to begin blood pressure measurement in the schools, the only place passed by all persons of the community. We should stress that all doctors should include blood-pressure measurement as a routine. We should now and then perform blood-pressure screenings mainly to inform the public of the importance of the measurements, but also to detect hypertensives who would not otherwise be found. The screening should be undertaken where people are i.e. in supermarkets, at the voting polls, etc.

And finally we should have on-going prospective randomized population studies not only to describe the changes in morbidity and mortality of cardiovascular diseases, but also to serve as bases for further research. I do hope that instead of controlling hypertension only with drugs we shall also be able to control it through other ways such as weight reduction, salt restriction and more physical exercise.

## References

1. Acheson, R.M. Blood pressure in national sample of U.S. adults: percentile distribution by age, sex and race. *Int. J. Epidemiol.* 2:293 1973
2. Becker P., Kamper-Jorgensen, F., Kristrup, J. & Pedersen, P.A.: The effect of the Danish Heart Society's blood-pressure campaign in 1975 as seen from general practice. *Ugeskr. Læg.* 138:495 1976.
3. Bee, J., Hannerfelt, S. & Wedervang, F.: The blood pressure in a population. *Acta med. scand. suppl.* 321 1957
4. Carlson, L.A. & Lindstedt, S.: The Stockholm prospective study. *Acta med. scand., Suppl.* 493, 1968
5. Hart, J.T.: Semicontinuous screening of whole community for hypertension. *Lancet* 2: 223 1970.
6. Johnson, R.C., Epstein, F.H. & Kjelsberg, M.O.: Distributions and familial studies of blood pressure and serum cholesterol levels in total community. Tecumseh, Michigan. *J. chron. Dis.* 18: 147 1965
7. Kannel, W.B., Gordon, T. & Schwartz, M.J.: Systolic versus diastolic blood pressure and risk of coronary heart disease. *Amer. J. Cardiol.* 27: 335 1971
8. Lew, E.A.: High blood pressure: other risk factors and longevity: The insurance viewpoint. *Amer. J. Med.* 55: 281 1973
9. Romington, R.D.: Control of premature mortality and morbidity by intervention on elevated blood pressure: The U.S. experience in: Ischaemic heart disease. The strategy of postponement (Eds. A. Tybjaerg Hansen, P. Schnohr & G. Rose) p. 64 F.A.D.J., Publishing Company Copenhagen 1977
10. Schnohr P.: Blood pressure in Copenhagen women 25-45 years of age. The Aarager women study 1973. *Ugeskr. Læg.* 138: 192, 1976.
11. Schnohr P. & Hansen, A.T.: A blood pressure information campaign including mass screening for hypertension in Copenhagen supermarkets. *Acta med. scand.* 199: 269 1976.
12. Schnohr P., Jensen, G., Nybo, J. & Hansen A.T.: The Copenhagen city heart study. A prospective cardiovascular population study of 20,000 men and women. *Ugeskr. Læg.* 139: 1921 1977
13. Wilhelmsen, L., Berglund, G. & Werkö, L.: Prevalence and management of hypertension in a general population sample of Swedish men. *Prev. Med.* 2: 57 1973



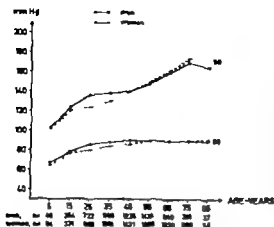


Fig. 1 Systolic and diastolic BP (right arm) in 13 704 men and women (median values) The supermarket campaign 1975

systolic pressure increases almost linearly with age, being higher in men than in women until the forties after which age the relation becomes reverse, a finding that is in agreement with the general trend in industrialized countries (1 3 4 5 6 7 8 13)

The cost of this screening including salary to the students (US\$ 7 per hour) transportation pamphlets cards and other materials was US\$ 12,000 or US\$ 0.49 per measurement. Of this amount US\$ 0.11 were for the BP pamphlet

In order to assess the effect of the campaign the number of patients visiting general practitioners during the week of the campaign and the succeeding week were registered and compared with the corresponding number during a control week six months later (2) Forty-eight practitioners participated in the campaign period and 24 in the control week also. All requests for blood pressure measurements were included, but patients in current control were excluded. Sixty per cent of the persons referred from the supermarkets had pressures that were still above our values for referral. Twenty three per cent of those referred had values that are generally accepted as requiring treatment. These values are as follows. for persons under 40 years of age a diastolic pressure above 100 mmHg for 40-49 a value above 105 for 50-59 a value above 110 and for persons 60

and over a value above 115 mmHg. This means that approximately 5% of the persons screened in the supermarkets at their second blood pressure measurement had values requiring treatment. The investigation further showed that there were 2.3 times as many visits to practitioners for measurement of blood pressure in the campaign period as in the control week and the practitioners' interest in blood pressure measurements was also greater during the campaign than during the control week six months later. Indicating that the effect declines with time. On the other hand the use of antihypertensive drugs increased significantly in Denmark the year following the campaign compared to the year before. The total drug consumption has been almost stable in Denmark during the last 10 years.

We felt that the main purposes of the supermarket screening namely information about a common and health threatening condition and finding persons with raised blood pressure were achieved. It must be stated that the campaign would not have had the same response without the help of news media. Almost every Dane heard or read about BP during this particular week in February 1975.

In February 1976 we began a prospective cardiovascular population study Øster

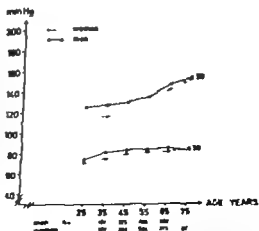


Fig. 2 Systolic and diastolic BP in 3 136 men and women (median values) The Copenhagen City Heart Study 1976.

broudersejelsen or the Copenhagen City Heart Study (12). The study population is a random sample of 20,000 men and women. By the end of August 1976, approximately 3,200 had been examined and the initial response rate was 69%.

Fig. 2 shows the median values for men and women and is unique because it is the first time to my knowledge that it has been found that through the entire lifespan women have lower blood pressures than men. The explanation could be that women use more antihypertensive drugs than men, and at all ages visit their doctors more frequently than men. Is the latter the reason why women live longer than men?

To conclude: The major problems in controlling high blood pressure are extremely common condition which often goes undetected, untreated or inadequately treated, are to get the symptom-free as well as the hypertensives with symptoms to accept medical care and to motivate them for lifelong follow-up and probably life long treatment.

To reach this goal we have to begin blood pressure measurement in the schools, the only place passed by all persons of the community. We should stress that all doctors should include blood-pressure measurement as a routine. We should now and then perform blood-pressure screenings mainly to inform the public of the importance of the measurements, but also to detect hypertensives who would not otherwise be found. The screening should be undertaken where people are i.e. in supermarkets, at the voting polls, etc.

And finally we should have on-going prospective randomized population studies not only to describe the changes in morbidity and mortality of cardiovascular diseases, but also to serve as bases for further research. I do hope that instead of controlling hypertension only with drugs we shall also be able to control it through other ways such as weight reduction, salt restriction and more physical exercise.

## References

1. Acheson, R.M. blood pressure in a national sample of U.S. adults: percentile distribution by age, sex and race. *Int. J. Epidemiol.* 2:293 1973
2. Backer  $\equiv$  Kamper Jørgensen, P. Kragstrup, J. & Pedersen, P.A.: The effect of the Danish Heart Society's blood-pressure campaign in 1975 as seen from general practice. *Ugeskr. Læg.* 138:495 1976.
3. Bee J. Hammerick S. & Wedervang, F. The blood pressure in a population. *Acta med. scand., suppl.* 121, 1957
4. Carlsson, L.A. & Lindstedt, S.: The Stockholm prospective study 1. *Acta med. scand., Suppl.* 493, 1968.
5. Hart, J.T. Semi-continuous screening of a whole community for hypertension, *Lancet* 2: 233, 1970.
6. Johnson, R.C., Epstein, F.H. & Kjelsberg, M.O. Distributions and familial studies of blood pressure and serum cholesterol levels in a total community. *Townsend, Michigan. J. Chron. Dis.* 18: 147 1965
7. Kannel, W.B., Gordon, T. & Schwartz, M.J. Systolic versus diastolic blood pressure and risk of coronary heart disease. *Amer. J. Cardiol.* 27: 335 1971
8. Lew E.A.: High blood pressure, other risk factors and longevity: The insurance viewpoint. *Amer. J. Med.* 55: 281 1973
9. Kessinghous, R.D. Control of pressure mortality and morbidity by intervention on elevated blood pressure. The U.S. experience in: *Ischaemic heart disease. The strategy of postponement* (Eds. A. Tybjaerg Hansen, P. Schnohr & O. Rose) p. 88 F.A.D.L., Publishing Company Copenhagen 1977
10. Schnohr P. Blood pressure in Copenhagen women 25-65 years of age. The Aragger women study 1973. *Ugeskr. Læg.* 136: 192, 1976.
11. Schnohr P. & Hansen, A.T. A blood pressure information campaign including mass screening for hypertension in Copenhagen supermarkets. *Acta med. scand.* 199: 269 1976.
12. Schnohr P. Jensen, O., Nyboe, J. & Hansen A.T. The Copenhagen city heart study. A prospective cardiovascular population study of 20,000 men and women. *Ugeskr. Læg.* 139: 1921 1977
13. Wilhelmsen, L., Berglund, G. & Werkö, L. Prevalence and management of hypertension in a general population sample of Swedish men. *Prev. Med.* 2: 57 1973

## Discussion

*Berglund.*

Schnohr has said that we should not start screening until we know whom we are to treat. I do not believe that we know today how we should treat a 12 year old with raised blood pressure.

*Schnohr.*

If a 12 year old has organic damage I think he should be treated. We have a school doctor system in Denmark which we do not fully utilize. Every year school doctors examine school children for hernia, but they never take the blood pressure.

# The Tromsø Heart Study

## The Consequences of Blood Pressure Screening in Men Aged 20-49 Years

DAG S. THELLE and OLAV H. FØRDE

From the Institutes of Clinical and Community Medicine,  
University of Tromsø, Norway

In 1974 6,593 men aged 20-49 years, i.e. 74.4% of the total population of that age in the municipality of Tromsø Northern Norway were examined with regard to coronary risk factors (1). Forty-eight of these subjects were reported to be on medical treatment for hypertension. Other subjects with systolic and diastolic blood pressure (BP) above certain limits were referred to six general practitioners who, on the basis of their own routine and judgement, decided if the subjects were in need of further examination or treatment (Fig. 1). The screening limits for this referral were either systolic BP equal to or above 160, 170 and 180 mmHg for age groups 20-29, 30-39 and 40-49 respectively or diastolic

BP values equal to or above 100, 105 and 110 for the same age groups. Sixty-one subjects had BP values which exceeded the limits, and 55 of them actually turned up for re-examination. Twenty-one had BP values which exceeded the systolic limits only 22 subjects exceeded the diastolic limits only and 12 subjects had BP values which exceeded both limits. At the re-examination by the general practitioner the subjects had diastolic blood pressure values which on average were 6.6 mmHg lower than at the screening while 7 subjects had higher readings at the re-examination.

The general practitioners found indication for medical treatment in 12 of the 55 subjects re-examined. Thirty-five were re-

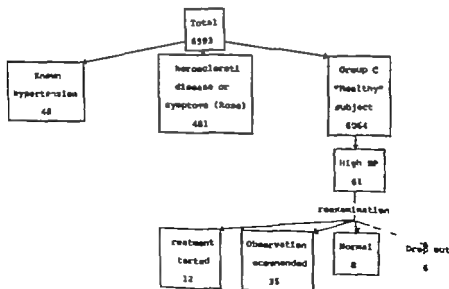


Fig. 1 Screening for hypertension in males aged 20-49 years.

Table 1 Results of blood pressure screening in males aged 20-49 years.

	Age groups (y)		
	20-29	30-39	40-49
Number in Group C ("Healthy") at screening	2244	2198	1622
Referral limits at screening			
Systolic	160	170	180
Diastolic	100	105	110
Number referred for re-examination	23	20	18
Number actually re-examined	21	16	18
Normotensives* at re-examination			
Number	5	2	1
Systolic BP			
Screen	156.8	152.0	170
Re-ex	129.0	137.5	140
Diastolic BP			
Screen	98.0	101.0	96.0
Re-ex	77.8	92.5	85.0
*Observation at re-examination			
Number	15	10	10
systolic BP			
Screen	148.8	163.0	174.6
Re-ex	143.3	154.0	157.5
Diastolic BP			
Screen	95.2	107.4	100.4
Re-ex	91.3	96.5	99.7
*Treatment* at re-examination			
Number	1	4	7
Systolic BP			
Screen	170	165.5	183.1
Re-ex	170	165.0	182.1
Diastolic BP			
Screen	78	111.5	117.4
Re-ex	70	106.3	115.7

commended for further observation, whereas 8 subjects were declared normotensive.

Table I gives the age specific BP values for these groups at the screening and at the re-examination.

As the result of the screening the number of subjects with medically treated hypertension increased from 48 to 60. This was a surprisingly low increase. Of course we also have to consider some benefit from having placed 35 subjects on observation. On the other hand, we do not know how many of these had already been told that they had a "high" blood pressure.

Both the recall frequency and the proportion of subjects in the different age-groups who were put on medical treatment, indicate that the screening limits could have been higher for the youngest subjects and perhaps lower for the oldest. Such a change would possibly have given us a higher benefit in the form of a few more hypertensives on treatment, but would obviously also have increased the number of re-examinations.

A natural conclusion from the present study is that blood pressure screening in men aged 20-49 years gives a rather low yield, and that such a program should not be started before the age of forty.

## References

1. Thelle, D.S., Ferde, O.H. Try E. & Lohmann, E.H. The Tromsø Heart Study: Methods and main results of the cross-sectional study. *Acta med. scand.* 200:107 1974.

## Discussion:

### Bergshovd

It seems to me that Norwegians from Tromsø are like the natives of the Kalahari desert—completely resistant to hypertension. Are there any other socio-economic variables and how is their sodium excretion? There is obviously a very low frequency of hypertension in Tromsø.

### Thelle

There is hardly any doubt that blood pressure values in the Tromsø study are lower than those in Oslo or in the Finnmark. The subjects were summoned to a medical polyclinic, where they waited for 20 to 50 minutes. They were not fasting and they were examined between 8 a.m. and 4 p.m. A few were examined at their place of work and their blood pressure was considerably higher. As for other variables, those we examined had high cholesterol and triglyceride levels, were quite heavy smokers, and took only moderate physical exercise.

### Beckgaard

I collected material on 1000 hypertensives over a 40 year period. One of the things that surprised me most was that so many reached such a high age. I have divided the patients into three groups according to the diastolic pressure, namely those over 110 mmHg, those between 110 and 100 mmHg, and those under 100 mmHg. The patients are grouped according to their blood pressure at a second examination about five years after hypertension was diagnosed. All the patients had rested for half-an-hour before the blood pressure was measured. In the men in the highest group there was a relatively high death-rate from heart disease, but not especially from myocardial infarction. Oddly enough, the death-rate from myocardial infarction was highest in the group with the lowest blood pressure. The number of cases of cerebral haemorrhage was not particularly large, but was greatest in the highest blood pressure group. Even patients in the highest group reached a relatively advanced age. In the women, there was a far greater frequency of cerebral haemorrhage in the highest group though it was not particularly high in the other groups. The number of deaths from heart disease was less than in the men, in fact, the greatest number of deaths was from causes unrelated to hypertension. The women reached a considerably higher age than the men, with a strikingly large number of deaths in the late 70's.

Table 1 Results of blood pressure screening in males aged 20-49 years

	Age groups (y)		
	20-29	30-39	40-49
Number in Group C ("Healthy") at screening	2244	2198	1622
Referral limits at screening			
Systolic	160	170	180
Diastolic	100	105	110
Number referred for re-examination	23	20	18
Number actually re-examined	21	16	18
"Normotensives" at re-examination			
Number	5	2	1
Systolic BP			
Screen	156.8	152.0	170
Re-ex	129.0	137.5	140
Diastolic BP			
Screen	98.0	101.0	96.0
Re-ex	77.8	92.5	85.0
"Observation" at re-examination			
Number	15	10	10
systolic BP			
Screen	148.8	163.0	174.6
Re-ex	143.3	154.0	157.5
Diastolic BP			
Screen	95.2	107.4	100.4
Re-ex	91.3	96.5	99.7
"Treatment" at re-examination			
Number	1	4	7
Systolic BP			
Screen	170	165.5	183.1
Re-ex	170	165.0	182.1
Diastolic BP			
Screen	78	111.5	117.4
Re-ex	70	106.3	115.7

# Threshold Values of Blood Pressure Based upon Mortality and Expected Effects of Treatment

HANS TH. WAALER

From the Health Service Research Group, Medical Research Council, Oslo, Norway

Epidemiological studies show continuously increasing mortality with increasing blood pressure. Excess mortality is observed already at pressure levels much below average values. No clearcut thresholds are suggested by mortality figures.

A ten year follow-up of mortality of a general population (Bergen, Norway) has been used to estimate such mortality rates. Changes in life expectancy ( $\Delta e$ ) were calculated as functions of sex, age and blood pressure (Table I). Treatment of hypertension is supposed to be able to retrieve some of these losses in years of life. This ability is assumed to be high (up to 80%) at young ages (25 years), and low (10-20%) at older ages (70 years).

Based on existing estimates of this ability which is admitted to be rather vague at present, one can calculate the potential benefit in terms of years of life as functions of sex, age and blood pressure (Table II).

To the extent that years of life are the benefit, this table should give a useful basis for setting priorities. The lower the age the higher the pressure, the higher the priority. The analysis also seems to give preference

to females. The reason for this is inherent in the method as the females have a general higher longevity than males already. This is undoubtedly in contrast with the general clinical attitude. This inconsistency would, however disappear if we excluded years of life above the age of 70.

If the figures in Table II were used for setting priorities it can be shown that 50% of the total blood pressure problem (covering all sex, age and pressure combinations with excess mortality) can be taken care of by treatment of only 4% of the individuals in the age groups 20-69 years.

Morbidity is not included in the analysis. However the arguments above hold true as long as the morbidity is proportional to the mortality.

Actual thresholds to be applied by the physician will depend finally upon his appreciation of such figures and findings and his opinion and knowledge of side-effects of treatment plus other clinical characteristics of the patient. However the figures presented might be a helpful indicator of where to concentrate the efforts.

Table I. Estimated loss of years of life, based upon 10 year follow-up of the population of Bergen, Norway

Age	Males						Females					
	Diastolic blood pressures mmHg											
	85	95	105	115	125	135	85	95	105	115	125	135
25	2.3	4.4	7.0	10.0	13.0	15.1	3.2	6.4	10.1	13.7	17.2	20.6
35	1.0	2.5	4.6	7.3	10.0	12.1	1.4	3.8	7.2	10.7	14.1	17.3
45		0.9	2.5	4.7	7.1	9.3	0.5	2.0	4.7	7.9	11.1	14.2
55			0.8	2.4	4.4	6.6	0.1	0.7	2.6	5.4	8.3	10.9
65				0.7	2.2	4.3			0.9	3.0	5.4	7.5



*Storm Mathisen.*

Bechgaard's work has given results that differ from the ones I have arrived at. The question that Bechgaard has brought up today is why does the prognosis look so promising and why do the patients in his material live so long when my young hypertonics die so early. I think it is partly because of the difference in age at the time of registration. In my material hypertension was registered before the patients had reached 46 whereas in Bechgaard's material they were about 10 years older at the time of registration. Most of the deaths in my material occurred in the age group 45 to 55. At this time of life the number of male deaths is ten times that of the normal population. For women it is eight times as much.

*Bechgaard.*

Yes, it is quite true that on the whole my patients have been older. As far as I remember the average age at the time of registration was 46 in Storm-Mathisen's material and in mine it was 53.

# Screening for Hypertension in 5 249 Copenhagen Males

FINN GYNTELBERG and LONE LAURIDSEN

From the Department of Internal Medicine C, Bispebjerg Hospital, Copenhagen, Denmark

In the autumn of 1970 a prospectively planned cardiovascular survey study was initiated on 5,249 middle-aged Copenhagen males. The main objectives of the study were to analyse:

1. Coronary risk factors in the population
2. The relationship between physical fitness and coronary risk factors.
3. The possible role of physical inactivity and poor physical fitness as coronary risk factor

All males studied were employed in public and private Copenhagen enterprises. The response rate was 87.3% and the examination of all subjects comprised:

1. A short interview on the basis of a questionnaire completed beforehand.
2. Measurement of arterial blood pressure.
3. Measurement of height and weight.
4. Indirect measurement of maximal aerobic power by the bicycle ergometer test introduced by Åstrand and Ryhming.

In a random subsample of the population venous blood was drawn for determination of serum cholesterol, hemoglobin and leucocyte count. In the same subsample of 370 males a 12 lead ECG was recorded.

Among these 5,249 men, 196 men had a hitherto unknown hypertension arbitrarily defined by blood pressure values above or equal to 165 mmHg systolic and 105 mmHg diastolic or above 110 mmHg diastolic irrespective of systolic blood pressure. These men with hitherto unknown hypertension were invited to participate in a clinical work-up in our out-patient clinic. At the beginning of the study however the clinic was not quite ready to receive the first hypertensive subjects detected by the

screening and for this reason 111 men could not be included in the study. These 111 men were all sent to their general practitioner for further clinical work-up. Eight men refused to participate in the work-up in our out-patient clinic. Thus all together 150 men with previously undetected hypertension had a clinical examination in our out-patient clinic during the spring and summer of 1971. Ninety-six of these were given antihypertensive drugs and all were told to see their own doctor for further follow-up and control of BP. The general practitioner was informed by letter about the hypertensive status.

Five years later 147 of these hypertensive patients were followed up (Table I). Three records had disappeared and could not be traced. Only 67% agreed to come for a re-examination in our out-patient clinic. Sixteen percent completed a questionnaire. In

Table I Distribution of the 150 screenees according to response at the 5-year follow-up

	No. of patients	% of total
Invited to follow-up	147	98.0
Agreed to come	101	67.3
Completed questionnaire	25	16.7
No response to two letters	12	8.0
Information from priv physicians	26	17.3
No information obtainable	8	5.3
BP-values obtained	123	82.0

Table II. Estimated gains through treatment in term of years of life.

Age	Males						Females					
	Diastolic blood pressures mmHg											
	85	95	105	115	125	135	85	95	105	115	125	135
25	1.5	2.8	4.6	6.5	8.4	9.8	2.1	4.2	6.6	8.9	11.2	13.4
35	0.4	1.1	2.0	3.1	4.3	5.2	0.6	1.6	3.1	4.6	6.0	7.5
45		0.3	0.8	1.4	2.1	2.8	0.2	0.6	1.4	2.4	3.4	4.2
55			0.2	0.5	0.9	1.3		0.2	0.5	1.1	1.7	2.2
65				0.1	0.2	0.4			0.1	0.3	0.5	0.8

# Discussion

*Wilhelmsen.*

Have the practical implications of these calculations been considered?

*Waele*

A panel consisting of Storm-Mathusen, Helgeland, Lund Larsen and Lund-Johansen are trying to reach a conclusion on the basis of this information. A report like the Swedish care programme will be published next year but with a slightly different approach.

# Screening for Hypertension in 5,249 Copenhagen Males

FINN GYNTELBERG and LONE LAURIDSEN

From the Department of Internal Medicine C, Bispebjerg Hospital, Copenhagen, Denmark

In the autumn of 1970 a prospectively planned cardiovascular survey study was initiated on 5,249 middle-aged Copenhagen males. The main objectives of the study were to analyse

1. Coronary risk factors in the population.
2. The relationship between physical fitness and coronary risk factors.
3. The possible role of physical inactivity and poor physical fitness as a coronary risk factor

All males studied were employed in public and private Copenhagen enterprises. The response rate was 87.3% and the examination of all subjects comprised:

1. A short interview on the basis of a questionnaire completed beforehand.
2. Measurement of arterial blood pressure.
3. Measurement of height and weight.
4. Indirect measurement of maximal aerobic power by the bicycle ergometer test introduced by Astrand and Ryhming

In a random subsample of the population venous blood was drawn for determination of serum cholesterol, hemoglobin and leucocyte count. In the same subsample of 370 males a 12 lead ECG was recorded.

Among these 5,249 men, 196 men had a hitherto unknown hypertension arbitrarily defined by blood pressure values above or equal to 165 mmHg systolic and 105 mmHg diastolic or above 110 mmHg diastolic irrespective of systolic blood pressure. These men with hitherto unknown hypertension were invited to participate in clinical work-up in our out-patient clinic. At the beginning of the study however the clinic was not quite ready to receive the first hypertensive subjects detected by the

screening and for this reason 38 men could not be included in the study. These 38 men were all sent to their general practitioner for further clinical work-up. Eight men refused to participate in the work-up in our out-patient clinic. Thus all together 150 men with previously undetected hypertension had a clinical examination in our out-patient clinic during the spring and summer of 1971. Ninety-six of these were given antihypertensive drugs and all were told to see their own doctor for further follow-up and control of BP. The general practitioner was informed by letter about the hypertensive status.

Five years later 147 of these hypertensive patients were followed up (Table I). Three records had disappeared and could not be traced. Only 67% agreed to come for a re-examination in our out-patient clinic. Sixteen percent completed a questionnaire. In

Table I Distribution of the 150 screeners according to response at the 5-year follow-up.

	No. of patients	% of total
Invited to follow-up	147	98.0
Agreed to come	101	67.3
Completed questionnaire	25	16.7
No response to two letters	12	8.0
Information from priv physicians	26	17.3
No information obtainable	8	5.3
BP-values obtained	123	82.0

Table II. Estimated gains through treatment in term of years of life

Age	Males						Females					
	Diastolic blood pressures mmHg											
	85	95	105	115	125	135	85	95	105	115	125	135
25	1.5	2.8	4.6	6.5	8.4	9.8	2.1	4.2	6.6	8.9	11.2	13.4
35	0.4	1.1	2.0	3.1	4.3	5.2	0.6	1.6	3.1	4.6	6.0	7.5
45		0.3	0.8	1.4	2.1	2.8	0.2	0.6	1.4	2.4	3.4	4.2
55			0.2	0.5	0.9	1.3		0.2	0.5	1.1	1.7	2.2
65				0.1	0.2	0.4			0.1	0.3	0.5	0.8

#### Discussion.

##### *Wilhelmsen.*

Have the practical implications of these calculations been considered?

##### *Wæler.*

A panel consisting of Storm Mathisen, Helgeland, Lund Larsen and Lund-Johansen are trying to reach a conclusion on the basis of this information. A report like the Swedish care programme will be published next year but with a slightly different approach.

# Screening for Hypertension in 5,249 Copenhagen Males

FINN GYNTELBERG and LONE LAURIDSEN

From the Department of Internal Medicine C, Bispebjerg Hospital, Copenhagen, Denmark

In the autumn of 1970 a prospectively planned cardiovascular survey study was initiated on 5,249 middle-aged Copenhagen males. The main objectives of the study were to analyze:

1. Coronary risk factors in the population.
2. The relationship between physical fitness and coronary risk factors.
3. The possible role of physical inactivity and poor physical fitness as a coronary risk factor.

All males studied were employed in public and private Copenhagen enterprises. The response rate was 87.3% and the examination of all subjects comprised:

1. A short interview on the basis of a questionnaire completed beforehand.
2. Measurement of arterial blood pressure.
3. Measurement of height and weight.
4. Indirect measurement of maximal aerobic power by the bicycle ergometer test introduced by Astrand and Ryhming.

In a random subsample of the population venous blood was drawn for determination of serum cholesterol, hemoglobin and leucocyte count. In the same subsample of 370 males 12 lead ECG was recorded.

Among these 5,249 men, 196 men had a hitherto known hypertension arbitrarily defined by blood pressure values above or equal to 165 mmHg systolic and 105 mmHg diastolic or above 110 mmHg diastolic irrespective of systolic blood pressure. These men with hitherto unknown hypertension were invited to participate in a clinical work-up in our out-patient clinic. At the beginning of the study however the clinic was not quite ready to receive the first hypertensive subjects detected by the

screening and for this reason 38 men could not be included in the study. These 38 men were all sent to their general practitioner for further clinical work-up. Eight men refused to participate in the work-up in our out-patient clinic. Thus all together 150 men with previously undetected hypertension had a clinical examination in our out-patient clinic during the spring and summer of 1971. Ninety-six of these were given antihypertensive drugs and all were told to see their own doctor for further follow-up and control of BP. The general practitioner was informed by letter about the hypertensive status.

Five years later 147 of these hypertensive patients were followed up (Table I). Three records had disappeared and could not be traced. Only 67% agreed to come for a re-examination in our out-patient clinic. Sixteen percent completed a questionnaire. In

Table I. Distribution of the 150 screenees according to response at the 5-year follow-up.

	No. of patients	% of total
Invited to follow-up	147	98.0
Agreed to come	101	67.3
Completed questionnaire	23	16.7
No response to two letters	12	8.0
Information from priv. physicians	26	17.3
No information obtainable	8	5.3
BP-values obtained	123	82.0

12 patients, who refused to participate, we could get further information from their private physicians. Thus it was possible to get reasonably good information on approximately 95% of the patients initially examined. Information on whether the non-responders were dead or alive could be obtained in all cases.

The patients who came to the out patient clinic appeared at least twice. From all subjects venous blood samples were drawn. ECG was recorded and thoracic X-ray was taken. BP was measured according to the recommendations of WHO. All subjects completed a standardised questionnaire. For a diagnosis of angina pectoris the criterion of chest pain and discomfort experienced during physical activity relieved by rest and/or nitroglycerin was used.

In Table II the number of deaths and cardio-vascular complications during the 5 years of observation are given. Seven had died from myocardial infarction and three from cerebro-vascular accidents. The

diagnosis of ischemic cerebral attack was based on a history of transient motor dysfunction of the extremities. One had undergone major surgery for aortic aneurism. One patient had a leg amputated because of femoral arterial stenosis.

Table III Blood pressure values in treated and untreated patients on re-examination.

	Blood pressure (mmHg)	No of patients	% of total
Treated No = 94	Diastolic > 100	43	28.7
	Systolic ≥ 165	13	8.7
	Diastolic ≤ 100 and Systolic < 165	38	25.3
Untreated No = 28	Diastolic > 100	11	7.3
	Systolic ≥ 165	5	3.3
	Diastolic ≤ 100 and Systolic < 165	12	8.0

Table II Number of deaths and cardiovascular complications

	No of patients	% of total
Deaths	10	6.7
Non-fatal myocardial infarction	6	4.1
Cardiac decompensation	1	0.7
Angina pectoris	13	8.7
Stroke	4	2.7
Transient ischemic cerebral attack	24	16.0
Vascular surgery	2	1.3
Hospitalized in the course of hypertension	9	6.0

#### Causes of deaths

No of myocardial infarction	7
No of cerebro-vascular accidents	2
No of others	1

Table III shows that 25.3% had well controlled BP on antihypertensive medication, 8% had normal BP without treatment. Thus only half a percent of the total number of the initially screened 5,249 men had benefited from the screening by having a high BP well controlled.

The prognosis of the hypertensive men found by screening as to mortality and incidence of major cardio-vascular events was rather poor. The mortality and number of major events were twice the expected rate. It should be taken into consideration that at the time of the screening all these men were able to work, had few symptoms and were carefully instructed to have their BP controlled.

It turned out however that twenty-six percent were not controlled at all. In approximately half the hypertensives the control was not satisfactory at the time of re-examination and many patients still had high BP after 5 years. The drugs which had been prescribed for these patients were beta-blocking agents, diuretics and

methyldopa. The costs of the drug treatment were approximately US\$ 100 per patient per year.

The poor patient compliance and BP control in this study cannot be due to economic factors because in Denmark everybody has a private physician whom he can see free of charge and 3/4 of the costs of drugs are paid for by public means.

#### **Discussion:**

##### *Schnohr*

I do not think that Gynzelberg's material gives grounds for being negative to the screening itself. The reason for the poor results was the poor follow-up. The patients were not treated well enough. Probably they were not motivated for treatment well enough, either

##### *Gynzelberg*

It is quite true that our screening was successful in so far as we did find those with raised blood pressure. However the great question is: What is the screening worth to those people who have taken part in it? I do not think we have shown that our screening has served any purpose. On the contrary it turned out much worse than we had expected. We had expected to find more people alive, fewer with complications and that the patients' blood pressure had been better treated. Screening is unethical if it is not followed up with effective treatment.

##### *Tybjærg Hansen*

Unfortunately screening is beginning to be an emotionally charged word. When a screening has not led to very much, there is no need to be miserable about it. Our supermarket screening had two purposes. Firstly to make the population aware of blood pressure. There are so many people who know nothing at all about their own physiology and we shall have to teach them. Secondly our screening was meant to show how easy it is to measure blood pressure. We must find new ways by which people can have their blood pressure mea-

sured acceptably and easily. Screening is not the only way. For example, doctors could organize the measurement of blood pressure by letting their nurses take it for every patient who comes for consultation. This is something that could easily be done.

##### *Wilhelmsen*

There are a few factors that are important. a) how blood pressure is measured by screening, and b) what do we do with the patients when screening reveals hypertension? I myself am not sure what should be done. Why are not patients adequately treated? The problems of hypertension should probably be approached more rationally in the population.



# Principles and Experiences of a Community Control Programme for Hypertension, as Part of the North Karelia Project

P. PUSKA, J. TUOMILEHTO, A. NISSINEN and J. SALONEN

From the Epidemiological Research Unit

Central Public Health Laboratory of Finland, Kuopio, Finland

A programme for community control of cardiovascular diseases (CVD) was established in 1972 in the county of North Karelia, a wide rural area with exceptionally high CVD mortality and morbidity and comprising some 180 000 inhabitants in Eastern Finland (1, 4, 5).

In the planning stage it was decided to start a comprehensive community programme, integrated with the service structure and the social organization of the community. The comprehensive intervention was planned to be multifactorial and to consist of both primary and secondary prevention (3).

The main objective of the programme was defined to be a decrease of the CVD morbidity and mortality among the North Karelian population and especially among the middle-aged and male population. The consideration of available epidemiological information from abroad and from Finland as well as the situation in North Karelia led to a heavy emphasis on primary prevention of the numerous disease attacks by a general reduction of the risk factors: smoking, serum cholesterol (i.e. change of diet) and high blood pressure among the population (3). The generally high level of these risk factors among the male population in the area has been shown, for example, by our studies (6).

Before planning the details of the programme, background information of the problem in the community was collected. A kind of "community diagnosis" was made. The community programme was designed to lead to the objectives, and the intervention was gradually implemented in a systematic way. The sub-programmes

were planned to contain the practical objectives and measures as well as the built-in continuous evaluation. For the evaluation and management of the programme an information system was to be established which had to be reliable enough but at the same time simple enough to be practicable for application in a large community.

In the comprehensive intervention the following methods have been incorporated: 1) increased health information, 2) training of personnel, 3) organization of services, and 4) environmental changes.

One essential sub-programme is the hypertension (HT) programme (7). The main objective of the hypertension programme is to lower high blood pressures in the entire population in order to reduce the complications, especially cerebral strokes and myocardial infarctions. The objectives cover: detection of hypertension cases, adequate diagnosis, treatment and follow-up of the patients. At the community level this implies blood pressure measurements for the whole population, systematic follow-up and drug treatment of the hypertensives. In order to reorganize the services, special dispensaries operated by public health nurses were to be established. A special regional hypertension register operating according to the WHO criteria was planned gradually to cover all the hypertensives in the community.

The programme is a national pilot programme of the Finnish health authorities to test the practicability and effect of the CVD community control. The practical programme is implemented as an integrated activity within the existing health services of the County which is reinforced

by extra persons and resources to organize the activities.

The aim of the evaluation of the entire programme and the hypertension programme as part of it is to demonstrate the feasibility and the effect of the programme, as well as to estimate the costs and to obtain a comprehensive picture of the process that takes place in the programme community (3).

The methods for the evaluation and the information system for monitoring the changes in the community include, for the main objectives, a myocardial infarction and stroke register and mortality and hospital data, and for the intermediate objectives random sample surveys covering risk factors and other information. A comprehensive survey is carried out in the programme community and in a matched reference community at the beginning and at the end of the five-year programme period (baseline survey 1972, terminal survey 1977). In addition a lot of other information is collected to follow the changes in the programme area.

The baseline survey and other baseline studies were conducted in the community before starting the intervention. Among the middle-aged population (aged 25-59) the prevalence of HT (160/95) was confirmed to be high (21%). In the younger age groups the males had a higher prevalence than females and in the older groups the females had more HT than the males. About half of the hypertensives were not aware about their condition and approximately 10% of the hypertensives were under adequate treatment.

After the baseline survey the programme to control HT in the community was established and integrated with the existing service structure. Blood pressure measurements were increased in connection with the usual health services and new screening activities were introduced (6). Everybody with established high blood pressure values (160 and/or 95 in three consecutive measurements) was registered according to the protocol of the WHO HT study (7). The hypertensives were treated and fol-

lowed by the local health centres. The follow-up was mostly carried out by trained nurses at the organized hypertension dispensaries with systematic health education. The patient was to see the treating physician at least once a year when the annual follow-up for the register was carried out.

During these years the feasibility of the programme has been good in the area with rather scarce medical resources. The good co-operation of the local population, community leaders and health personnel has been experienced in many ways. For example, participation rates in the surveys averaged 90 per cent.

Since the beginning of the programme blood pressure measurements gradually increased so that they covered practically the whole population. The number of registered hypertensives increased accordingly so that at the end of 1976 nearly 17,000 hypertensives were registered, which approaches 9% of the total population. Out of these subjects more than half became aware of their condition only during the programme. The frequency of control visits of those with known hypertension increased so that it led within the first years to an adequate situation for practically every known hypertensive.

An interim study showed also that the adherence to the follow-up and to the treatment was good. For example during the first year only 1% of the registered hypertensives missed their annual follow-up visit. The adherence to the treatment was then 94%.

After 4.5 years of the intervention the percentage of the middle-aged population under antihypertensive drug treatment increased among the males from 3 to 11 and among the females from 9 to 13 in the whole community. According to the register the percentage of normotensive subjects in the HT register increased during the first year from 12 to 28 and at the fourth follow-up to 38. The mean change in blood pressure during the first year was 15 mmHg reduction in the systolic and a 6 mmHg reduction in the diastolic blood pressure for those patients who had had

# Principles and Experiences of a Community Control Programme for Hypertension, as Part of the North Karelia Project

P. PUSKA, J. TUOMILEHTO, A. NISSINEN and J. SALONEN

From the Epidemiological Research Unit,  
Central Public Health Laboratory of Finland Kuopio, Finland

A programme for community control of cardiovascular diseases (CVD) was established in 1972 in the county of North Karelia, a wide rural area with exceptionally high CVD mortality and morbidity and comprising some 180 000 inhabitants in Eastern Finland (1, 4, 5).

In the planning stage it was decided to start a comprehensive community programme integrated with the service structure and the social organization of the community. The comprehensive intervention was planned to be multifactorial and to consist of both primary and secondary prevention (3).

The main objective of the programme was defined to be a decrease of the CVD morbidity and mortality among the North Karelian population and especially among the middle-aged and male population. The consideration of available epidemiological information from abroad and from Finland as well as the situation in North Karelia, led to a heavy emphasis on primary prevention of the numerous disease attacks by a general reduction of the risk factors, smoking, serum cholesterol (i.e. change of diet) and high blood pressure among the population (3). The generally high level of these risk factors among the male population in the area has been shown for example by our studies (6).

Before planning the details of the programme, background information of the problem in the community was collected. A kind of "community diagnosis" was made. The community programme was designed to lead to the objectives and the intervention was gradually implemented in a systematic way. The sub-programmes

were planned to contain the practical objectives and measures as well as the built-in continuous evaluation. For the evaluation and management of the programme an information system was to be established which had to be reliable enough, but at the same time simple enough to be practicable for application in a large community.

In the comprehensive intervention the following methods have been incorporated: 1) increased health information, 2) training of personnel, 3) organization of services and 4) environmental changes.

One essential sub-programme is the hypertension (HT) programme (7). The main objective of the hypertension programme is to lower high blood pressures in the entire population in order to reduce the complications especially cerebral strokes and myocardial infarctions. The objectives cover detection of hypertension cases, adequate diagnosis, treatment and follow-up of the patients. At the community level this implies blood pressure measurements for the whole population, systematic follow-up and drug treatment of the hypertensives. In order to reorganize the services special dispensaries operated by public health nurses were to be established. A special regional hypertension register operating according to the WHO criteria was planned gradually to cover all the hypertensives in the community.

The programme is a national pilot programme of the Finnish health authorities to test the practicability and effect of the CVD community control. The practical programme is implemented as an integrated activity within the existing health services of the County which is reinforced

# Epidemiology and Treatment of Hypertension in North Karelia with Special Reference to Detection for Hypertension

JAAKKO TUOMILEHTO, PEKKA PUSKA, AULIKKI NISSINEN and JARMO VIRTAMO

From the Epidemiological Research Unit,  
Central Public Health Laboratory of Finland, University of Kuopio, Finland

The purpose of the baseline survey of the North Karelia Project was to measure the level of cardio-vascular risk factors. The hypertension (HT) data obtained in the baseline survey are used to evaluate the hypertension programme of the North Karelia Project by comparing them with those gathered in the terminal survey after 5-year intervention (3). On the other hand the information concerning the prevalence, detection and treatment of HT was utilized in planning the programme (2).

The survey was carried out in 1972. From the population aged 25 to 59 a 6.5 per cent random sample was drawn from the National Population Register. The blood pressures of 4,275 persons (2,095 men and 2,180 women) from the representative population sample were measured. Participation rate was 90%.

The level of systolic blood pressure (BP) rose with increasing age among men and women. In the age group under 45 men had a higher level than women, but the rise with age was greater among women. The same applies also to diastolic BP which however varied less.



Fig. 1. Percentage of hypertensives\* according to age and sex.

Blood pressure  $\geq 160/95$  mmHg. Aged 30-59  
 $\geq 150/90$  mmHg. Aged 25-29



Fig. 2. Percentage of estimated need for treatment\* for hypertension according to age and sex. Blood pressure  $\geq 175/110$  or under antihypertensive drug treatment.

The casual systolic BP was over 160 mmHg in 23% of males and 31% of females. The casual diastolic BP was at least 95 mmHg in 34% of males and 36% of females. Under the age 40 more men than women were hypertensive, after the age 40 the opposite was the case (Fig. 1). The number of persons needing treatment has been estimated arbitrarily (Fig. 2).

Sixteen percent of women and 6% of men aged 45-59 used antihypertensive drugs. In the age groups under 45 there was no significant difference between the sexes. Three percent of all men and 9% of all women were under treatment. Fifteen percent of all men and 34% of all women had been informed of having elevated BP. HT had been detected at a visit to a doctor in about half of the cases. During stay at a hospital or by screening, HT was detected more frequently in men than women. A public health nurse had discovered two fifths of all female hypertensive cases and the vast majority of female hypertensives aged 25-44 had been diagnosed by public health nurses. The proportion of cases diagnosed in hospital increased and that of cases detected by screening decreased with

this follow-up. It must be noted that 65% of these hypertensives were already under drug treatment at the time of the registration.

The preliminary information from the stroke register shows that the annual stroke incidence rates were reduced in 1975 to 1.9 for males and 1.8 for females in the 25-74 age group calculated per 1000 inhabitants. No age specific trend was noticed in this reduction which became evident during the third year of the intervention, i.e. 1974. The 3 week case fatality rates of the registered strokes were reduced from 1972 to 1975 from 23% to 17% among the males and from 27% to 10% among the females. During the same period the same system of registration showed no change in the incidence rates of acute myocardial infarction (MI). In the total and MI mortality rates of middle-aged males and females during the three first years of the programme in North Karelia a reduction can be seen compared with the two pre-programme years.

The presented evaluation of the programme is preliminary. Only the final evaluation using different data sources and a matched reference area will reveal the final effect of the programme. It can, however, be already now stated that the feasibility of this community programme has been good and it has needed minimal amount of extra resources. The interim evaluation indicates a clear improvement in the blood pressure situation of the population and it is possible that this is associated with a reduction in the occurrence of cerebral strokes in the community.

## References

- 1 Keys, A. (ed.): Coronary heart disease in seven countries. *Circulation (suppl.)* 16, 1 1970.
- 2 Puska, P.: Sydän ja verisuonitautiin altistuman kuoletusriskin alustelliset erot I. *Soom laak* 1 27 3071 1972.
- 3 Puska, P.: The North Karelia project, a programme for community control of cardiovascular diseases. Publication of the University of Kuopio. Community Health-series A. 1/1974.
- 4 Puska, P., Aho K. & Salmi K.: Seirastavuus elvohalvauksien Suomessa. *Duodecim* 90: 965 1974.
- 5 Puska, P. & Mustaniemi, H.: Incidence and presentation of myocardial infarction in North Karelia, Finland. *Acta med. scand.* 197 211 1975.
- 6 Rimpelä, M., Puska, P., Sievers, K., Tuomilehto J., Virtamo J., Karjalainen Y. & Prunnila T.: The baseline survey of the North Karelia project. Study design and prevalence of major CHD risk indicators. *Sos laaket* 1 2, 97 1974.
- 7 Tuomilehto J.: Feasibility of a community programme for control of hypertension. A part of the North Karelia project. Publications of the University of Kuopio, Community Health-series A. 2/1975.

# Epidemiology and Treatment of Hypertension in North Karelia with Special Reference to Detection for Hypertension

JAAKKO TUOMILEHTO, PEKKA PUSKA, AULIJKI NISSINEN and JARMO VIRTANIO  
From the Epidemiological Research Unit,  
Central Public Health Laboratory of Finland, University of Kuopio, Finland

The purpose of the baseline survey of the North Karelia Project was to measure the level of cardio-vascular risk factors. The hypertension (HT) data obtained in the baseline survey are used to evaluate the hypertension programme of the North Karelia Project by comparing them with those gathered in the terminal survey after 5-year intervention (3). On the other hand the information concerning the prevalence, detection and treatment of HT was utilized in planning the programme (2).

The survey was carried out in 1972. From the population aged 25 to 59 a 6.5 per cent random sample was drawn from the National Population Register. The blood pressures of 4,275 persons (2,095 men and 2,180 women) from the representative population sample were measured. Participation rate was 90%.

The level of systolic blood pressure (BP) rose with increasing age among men and women. In the age group under 45 men had a higher level than women, but the rise with age was greater among women. The same applies also to diastolic BP which however varied less.



Fig. 1 Percentage of hypertensives according to age and sex.

Blood pressure  $\geq 160/95$  mmHg. Aged 30-39  
 $\geq 150/90$  mmHg. Aged 25-29



Fig. 2. Percentage of estimated need for treatment for hypertension according to age and sex. Blood pressure  $\geq 175/110$  or under antihypertensive drug treatment.

The casual systolic BP was over 160 mmHg in 23% of males and 31% of females. The casual diastolic BP was at least 95 mmHg in 34% of males and 36% of females. Under the age 40 more men than women were hypertensive, after the age 40 the opposite was the case (Fig. 1). The number of persons needing treatment has been estimated arbitrarily (Fig. 2).

Sixteen percent of women and 6% of men aged 45-59 used antihypertensive drugs. In the age groups under 45 there was no significant difference between the sexes. Three percent of all men and 9% of all women were under treatment. Fifteen percent of all men and 34% of all women had been informed of having elevated BP. HT had been detected at a visit to a doctor in about half of the cases. During stay at a hospital or by screening, HT was detected more frequently in men than women. A public health nurse had discovered two fifths of all female hypertensive cases and the vast majority of female hypertensives aged 25-44 had been diagnosed by public health nurses. The proportion of cases diagnosed in hospital increased and that of cases detected by screening decreased with

**Increasing age among men** The proportion of hypertensives detected under the age of 30 was greater among women than among men

About half of the men and women who were aware of HT reported having used antihypertensive drugs at one time or another (Table 1). Every fifth man and every fourth woman had used antihypertensive drugs during the week preceding the examination. The proportion of men using drugs was greater than that of women in the age group 25-44, whereas in the age group 45-59 women used drugs more frequently than men.

Half of the men and women who had used antihypertensive drugs had been under treatment for less than two years. Only one fifth of the men and one third of the women who had used drugs had been under drug treatment for more than five years. Approximately one-third of the men and women who had used antihypertensive drugs had been continually under drug treatment. Half of those examined reported that there had been breaks in drug treatment. One quarter of the men and two fifths of the women had been living without drug treatment for more than five years. Only very few of those who had discontinued antihypertensive drug treatment were normotensive at the moment of the examination.

A majority (60%) of those examined had had their BP checked at least once within the past six months. In 5% BP had not been measured during the past five years. One third of those examined reported that they had had their BP checked at regular intervals. Those who had abandoned regular check-ups said that they had done so because of their doctor's instructions; one tenth reported that work had obstructed regular measurements. Those who had discontinued antihypertensive drug treatment said that they had followed their doctor's instructions in doing so; in a few cases side effects of the drugs had caused discontinuation. Every fifth man and every twentieth woman said that they had forgotten to renew the prescriptions for one reason or another.

According to the criteria for HT 20% of men and 26% of women in the baseline survey were classified as hypertensives. Almost half of the hypertensive men and women were aware of their condition and about half of them had been under treatment at one time or another. At the time of the examination two fifths of the men and one half of the women who had been under treatment were still being treated. Among the subjects who had been told about their HT drug treatment, normotension was restored in 13% of the males and 10% of the females.

Table 1. Percentage of unknown, untreated and inadequately treated hypertensives in North Karelia in 1972.

	males		females	
Representative population sample	2095	(100%)	2180	(100%)
Hypertensives <sup>1</sup> in the sample	419	(20%)	567	(26%)
Not aware of their hypertension	230/419	(55%)	301/567	(53%)
Never treated (out of those aware)	94/189	(50%)	122/266	(46%)
Not under drug treatment (out of the treated)	60/95	(60%)	72/144	(50%)
Not normotensive out of the treated	20/35	(55%)	53/72	(77%)

Blood pressure  $\geq 160/\geq 95$  aged 30-59 and  
 $\geq 150/\geq 90$  aged 25-29  
 or under antihypertensive drug treatment

Our results seem to have confirmed that the general level of BP is high in North Karelia higher than in other parts of Finland (1). The blood pressure level of men under 45 years is clearly higher than that of women. This applies both to systolic and diastolic pressures. The mean BP does not rise much with age in men but the rise is steep in women.

The prevalence of HT is 20% among men and 26% among women. Also here the clear age specific differences are seen. This means that the management of HT in the community should cover men at an earlier age than women. Furthermore middle-aged men run a much higher risk of cardiovascular diseases. This higher risk can partly be referred to a higher BP level in younger age groups. However our findings concerning treatment of HT are not very promising. In 1972, before the intervention of the North Karelia Project more women were under treatment and there was no difference between sexes in younger age groups. Thus the treatment of young men has definitely been inadequate.

To provide long-term treatment for HT in North Karelia has been as problematic as everywhere else in the world (4). The main problem seems to be that treatment is discontinued in most cases within one or two years. The reason is to be found in our health care system, especially in doctors who have not been very active in keeping patients on a long-term treatment and follow-up.

According to our experiences measurement of BP was carried out on a wide scale already before special intervention. In North Karelia before the intervention most cases were detected by a doctor's examination and rather many in a hospital. This was true especially for men. In women the follow-up of the hypertensive cases has apparently been more successful because of the active role of public health nurses. High BP has been found in women earlier than in men in spite of the fact that the BP level in men is higher in the younger age groups.

Our results show that even in women the

effect of all measures in the management of HT has been unsatisfactory. What is needed is primarily a systematic way to organize the follow-up and treatment services, but also services for early detection of HT especially in young men.

## References

1. Aromaa, A., Epidemiology of hypertension. *Soa. Ital. Aik.* 1: 10:320, 1972.
2. Paska, P., Koskela, K., Pakarinen, H., Pussalainen, P., Solinon, V. & Tuomilehto, J. The North Karelia Project. A programme for control of cardiovascular diseases. *Scand. J. soc. Med.* 4: 471 1976.
3. Tuomilehto, J., Paska, P., & Nieminen, A., Hypertension programme of the North Karelia Project. *Scand. J. soc. Med.* 4: 57 1976.
4. World Health Organisation: Community control of stroke and hypertension. Report of a WHO meeting. CVD/72.1 1971.

## Discussion:

### *Pasborg Petersen:*

Do you have any suggestions or knowledge of factors which might be responsible for the very high frequency of hypertension in the North Karelia district? Compared with the study from Tromsø the frequency is ten to twenty times as high. Dull, who studied the frequency of hypertension in some Japanese island, could demonstrate that there was a clear association between high salt intake and high frequency of hypertension. Do you have any suggestions as to such factors, and is the frequency of hypertension the only factor responsible for the high incidence of cardiovascular disease in North Karelia?

### *Tuomilehto:*

We have studied possible background factors for essential hypertension in North Karelia. We have used such variables as body weight, physical exercise and some socio-economic factors. We found that there was a clear association between hypertension and socio-economic factors such as family income and education. There was also an association with body weight but all these factors could explain only about twenty per cent of the variation



of blood pressure. We have not done any studies until now about salt consumption but during our terminal survey we are going to study this question on the basis of urinary salt excretion. Karvonen and Keys in their sample study in Finland found that salt consumption in eastern Finland is rather high

#### *Puska*

High cardiovascular risk in North Karelia from our prospective studies seem to depend on three factors serum cholesterol, smoking, and high blood pressure. The North Karelian population has the highest known combined level of these risk factors. Especially serum cholesterol level is high. As far as hypertension is concerned there are some other populations of similar levels and smoking habits in North Karelia are not exceptional

# Follow up of the Hypertensive Patients in North Karelia and some Results from the Hypertension Register

AULIKKI NISSINEN, JAAKKO TUOMILEHTO and PEKKA PUSKA  
From the Epidemiological Research Unit,  
Central Public Health Laboratory of Finland, University of Kuopio, Finland

Since its establishment in 1972 the North Karelia Project has continually followed all hypertensive patients in the whole community through a hypertension (HT) register (4, 8). Once having entered the register the patients have had an annual examination. In 1977 the number of patients on the register was 17 115. The criteria for HT have been: 150 and/or 95 mmHg (29 years), 160 and/or 95 mmHg (30-64 years), 170 and/or 95 mmHg (65+ years), or already receiving drug treatment for hypertension.

The main goal of this register has been to maintain patients in treatment (3) and to get information about the progress of the HT programme. However the final evaluation of the programme as part of the project will be made by using the terminal survey (1).

Here we describe the progress of the treatment and its effect on blood pressure

(BP) of registered patients during the first four years of the register.

Out of the 16,967 registered patients 6,307 were males and 10 661 females. About 60% of these men and 40% of the women were under 55. 16% of males and 30% of females registered were over 65. Among registered patients 77% have been followed for more than one year, 63% for more than two years, 42% for more than three years and 15% for more than four years.

The majority of patients have been referred to the register as known HT cases and half of the patients were aware of their HT before the establishment of the North Karelia Project in 1972 (Table I).

Half of the registrants had previously been or were still under drug treatment. Eighteen percent have been identified by mass screening. At the initial examination 98% of the patients in the register were

Table I. Time of awareness of high blood pressure on entering the hypertension register

Time of awareness of high blood pressure	The registration year				1976- April 1977	Total
	1972 (%)	1973 (%)	1974 (%)	1975 (%)	(%)	(%)
1971 or before	81	57	38	34	32	49
1972	19	18	10	9	8	13
1973		25	19	13	10	16
1974			34	20	9	13
1975				28	14	11
1976-April 1977					28	3
Total	100	100	100	100	100	100
Number	2684	5296	4371	2835	1751	16957

of blood pressure. We have not done any studies until now about salt consumption, but during our terminal survey we are going to study this question on the basis of urinary salt excretion. Karvonen and Keys in their sample study in Finland found that salt consumption in eastern Finland is rather high

#### *Puska*

High cardiovascular risk in North Karelia from our prospective studies seem to depend on three factors: serum cholesterol, smoking, and high blood pressure. The North Karelian population has the highest known combined level of these risk factors. Especially serum cholesterol level is high. As far as hypertension is concerned there are some other populations of similar levels and smoking habits in North Karelia are not exceptional.

# Follow up of the Hypertensive Patients in North Karelia and some Results from the Hypertension Register

AULIHKI MISSINEN, JAAKKO TUOMILEHTO and PEKKA PUSKA  
From the Epidemiological Research Unit,  
Central Public Health Laboratory of Finland, University of Kuopio, Finland

Since its establishment in 1972 the North Karelia Project has continually followed all hypertensive patients in the whole community through a hypertension (HT) register (4-8). Once having entered the register the patients have had an annual examination. In 1977 the number of patients on the register was 17 115. The criteria for HT have been: 150 and/or 93 mmHg (29 years), 160 and/or 95 mmHg (30-64 years), 170 and/or 95 mmHg (65+ years), or already receiving drug treatment for hypertension.

The main goal of this register has been to maintain patients in treatment (3) and to get information about the progress of the HT programme. However the final evaluation of the programme as part of the project will be made by using the terminal survey (1).

Here we describe the progress of the treatment and its effect on blood pressure

(BP) of registered patients during the first four years of the register.

Out of the 16,967 registered patients 6,307 were males and 10,661 females. About 60% of these men and 40% of the women were under 55. 16% of males and 30% of females registered were over 65. Among registered patients 77% have been followed for more than one year, 63% for more than two years, 42% for more than three years and 15% for more than four years.

The majority of patients have been referred to the register as known HT cases and half of the patients were aware of their HT before the establishment of the North Karelia Project in 1972 (Table I).

Half of the registrants had previously been or were still under drug treatment. Eighteen percent have been identified by mass screening. At the initial examination 98% of the patients in the register were

Table I Time of awareness of high blood pressure on entering the hypertension register

Time of awareness of high blood pressure	The registration year				1976- April 1977	Total
	1972 (%)	1973 (%)	1974 (%)	1975 (%)	(%)	(%)
1971 or before	81	57	38	34	32	49
1972	18	18	10	9	8	13
1973		25	19	13	10	16
1974			34	20	9	13
1975				24	14	6
1976- April 1977					28	3
Total	100	100	100	100	100	100
Number	2684	5296	4371	2835	1751	16937

Table II Proportion of registered patients under antihypertensive drug treatment in the initial and annual follow-up examinations, by sex

Time of examination	males (%)	females (%)	total (%)
Initial examination	51	59	56
1 Annual follow-up	68	75	73
2 Annual follow up	75	79	77
3 Annual follow-up	80	86	84
4 Annual follow up	80	88	86

diagnosed as essential hypertensives and only in 1% a certain cause for secondary HT was found

Local general practitioners have been responsible for the treatment. Each health centre has established an HT dispensary which is managed by a public health nurse. Patients visit the nurse about 3-6 times and the doctor about 1-2 times per year. The doctor and the nurse have a close co-operation so that the nurse can consult the doctor whenever necessary.

Registration of patients was decided by a doctor after three consecutive BP measurements. Doctors have filled in the initial record forms. The registration of patients has been continual from 1972 to spring 1977. The coordination centre of the North Karelia Project asked the patients two months before the annual follow-up date to visit their doctor. The aim of this procedure was to avoid drop-outs and to make it

possible for the patient to combine other medical problems with the annual follow-up visit. With this method it has been possible to get information on about 90% of all the patients in the register in each follow-up year.

A doctor personally or a qualified assistant has measured BP's for the register data according to the recommendation of the North Karelia Project. This requires measurement after 5-10 minutes rest in a sitting position. The diastolic BP was recorded as the fifth phase of Korotkoff's sounds.

During the first follow-up year 44% of the registered patients had their BP measured more than 7 times by either a doctor or a public health nurse. Later on the frequency of the measurement decreased.

The proportion of patients under treatment has increased during the follow-up period so that after 3 years follow-up 84%

Table III Percentage of normotensives in annual follow-up examinations according to different criteria.

Time of examination	The criteria of hypertension (mmHg)			
	A) (%)	DBP < 100 (%)	DBP < 105 (%)	SBP < 160 (%)
Initial examination	12	54	62	34
1 Follow-up	28	72	80	53
2 Follow-up	33	77	85	57
3 Follow-up	36	80	88	56
4 Follow-up	38	83	89	54

A) < 29 years < 150/90  
 30-64 years < 160/95  
 > 65 years < 170/95

were under drug treatment (Table II). The average BP of the patients decreased during all the follow-up years being most marked during the first year (Fig. 1). Proportion of the normotensive patients in the annual follow-up examinations increased clearly the year after the first follow-up year (Table III).

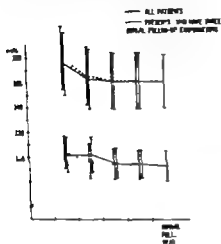


Fig. 1 Changes of the average BP in all registered patients and in patients who have since been followed-up continuously.

The first annual follow-up was missed in 13% of the cases. Approximately one-third was due to death, emigration, etc. In the second annual follow-up this percentage was 10, in the third 5 and in the fourth 1.

The 17 115 patients in the register constitute 9.7% of the total population of North Karelia. The proportion of males in the register has continually increased and now the proportion of males and females is as expected. This shows that the register has succeeded in covering also the middle-aged males who have especially high CVD risk.

Practically all hypertensives in North Karelia are today aware of their HT and most of them are also registered. Half of the patients having entered the register have become aware of their HT during the 5-year intervention period of the North Karelia Project.

The establishment of the register has been feasible owing to very active co-opera-

tion with general practitioners and public health nurses in the health centres. Registration of the patients as well as the follow-up have been performed by them. The follow-up has been successful, the number of drop-outs has been small. More than half the drop-outs in the follow-up has been due to some known reason like death or emigration (5). This good patient compliance can be ascribed to the HT dispensary system run by public health nurses.

A great proportion of the patients in the register have become normotensive. The continuous decrease in average BP is a sign that the treatment is becoming more and more adequate. It must be remembered that even partial decrease of high BP reduces the risk of serious cardiovascular complications (2, 6, 7).

#### References

1. Puska, P., Korkala, K., Pekurinen, H., Paasinen, P., Solonen, V. & Tuomilehto, J. The North Karelia Project. A programme for control of cardiovascular diseases. *Scand. J. soc. Med.* 4:57 1976.
2. Taguchi, J. & Fries, E. Partial reduction of blood pressure and prevention of complications in hypertension. *New Eng. J. Med.* 291:329 1974.
3. Tuomilehto, J. Feasibility of community programme for control of hypertension. A part of the North Karelia Project. Publications of the University of Kuopio. Community Health-series A.2/1975.
4. Tuomilehto, J., Puska, P. & Nissinen, A. Hypertension programme of the North Karelia Project. *Scand. J. soc. Med.* 4:67 1976.
5. Tuomilehto, J., Rajala, A.-L., & Puska, P. A study on the drop-outs of the hypertension register of the North Karelia Project. *Comm. Health* 7:149 1976.
6. Veterans Administration Study Group on Antihypertensive Agents: Effects of treatment on morbidity in hypertension. Results in patients with diastolic blood pressures averaging 115 through 129 mmHg. *J. Amer. med. Ass.* 202:1028, 1967.
7. Veterans Administration Study Group on Antihypertensive Agents: Effects of treatment on morbidity in hypertension. II. Results in patients with diastolic blood pressures averaging 90 through 114 mmHg. *J. Amer. med. Ass.* 213:1143 1970.
8. World Health Organization: Community control of stroke and hypertension. Report of WHO meeting. CVD/72.1 1971.

Table II Proportion of registered patients under antihypertensive drug treatment in the initial and annual follow-up examinations by sex.

Time of examination	males (%)	females (%)	total (%)
Initial examination	51	59	56
1 Annual follow up	68	75	73
2 Annual follow up	75	79	77
3 Annual follow up	80	86	84
4 Annual follow up	80	88	86

diagnosed as essential hypertensives, and only in 1% a certain cause for secondary HT was found

Local general practitioners have been responsible for the treatment. Each health centre has established an HT dispensary which is managed by a public health nurse. Patients visit the nurse about 3-6 times and the doctor about 1-2 times per year. The doctor and the nurse have a close co-operation so that the nurse can consult the doctor whenever necessary.

Registration of patients was decided by a doctor after three consecutive BP measurements. Doctors have filled in the initial record forms. The registration of patients has been continual from 1972 to spring 1977. The coordination centre of the North Karelia Project asked the patients two months before the annual follow-up date to visit their doctor. The aim of this procedure was to avoid drop-outs and to make it

possible for the patient to combine other medical problems with the annual follow up visit. With this method it has been possible to get information on about 90% of all the patients in the register in each follow-up year.

A doctor personally or a qualified assistant has measured BP's for the register data according to the recommendation of the North Karelia Project. This requires measurement after 5-10 minutes rest in a sitting position. The diastolic BP was recorded as the fifth phase of Korotkoff's sounds.

During the first follow up year 44% of the registered patients had their BP measured more than 7 times by either a doctor or a public health nurse. Later on the frequency of the measurement decreased.

The proportion of patients under treatment has increased during the follow-up period so that after 3 years follow-up 84%

Table III Percentage of normotensives in annual follow-up examinations according to different criteria.

Time of examination	The criteria of hypertension (mmHg)			
	A) (%)	DBP < 100 (%)	DBP < 105 (%)	SBP < 160 (%)
Initial examination	12	54	62	34
1 Follow-up	28	72	80	53
2 Follow up	33	77	85	57
3 Follow up	36	80	88	56
4 Follow-up	38	83	89	54

A) < 29 years < 150/90

30-64 years < 160/95

> 65 years < 170/95

were under drug treatment (Table II). The average BP of the patients decreased during all the follow-up years being most marked during the first year (Fig. 1) Proportion of the normotensive patients in the annual follow-up examinations increased clearly the year after the first follow-up year (Table III).

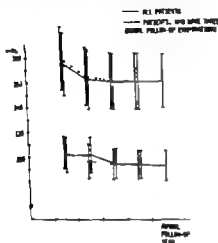


Fig. 1 Changes of the average BP in all registered patients and in patients with three annual follow-up examinations.

The first annual follow-up was missed in 13% of the cases. Approximately one-third was due to death, emigration, etc. In the second annual follow-up this percentage was 10% in the third 5 and in the fourth 1.

The 17 115 patients in the register constitute 9.7% of the total population of North Karelia. The proportion of males in the register has continually increased and now the proportion of males and females is as expected. This shows that the register has succeeded in covering also the middle-aged males who have especially high CVD risk.

Practically all hypertensives in North Karelia are today aware of their HT and most of them are also registered. Half of the patients having entered the register have become aware of their HT during the 5-year intervention period of the North Karelia Project.

The establishment of the register has been feasible owing to very active co-opera-

tion with general practitioners and public health nurses in the health centres. Registration of the patients as well as the follow-up have been performed by them. The follow-up has been successful, the number of drop-outs has been small. More than half the drop-outs in the follow-up has been due to some known reason like death or emigration (5). This good patient compliance can be ascribed to the HT dispensary system run by public health nurses.

A great proportion of the patients in the register have become normotensive. The continuous decrease in average BP is a sign that the treatment is becoming more and more adequate. It must be remembered that even partial decrease of high BP reduces the risk of serious cardiovascular complications (2, 6, 7).

## References

1. Puska, P., Koskela, K., Pekariinen, H., Puska-Mäkelinen, P., Soukka, V. & Tuomilehto, J. The North Karelia Project. A programme for control of cardiovascular diseases. *Scand. J. soc. Med.* 4:57 1976.
2. Taguchi, J. & Freis, E. Partial reduction of blood pressure and prevention of complications in hypertension. *New Eng. J. Med.* 291:329 1974.
3. Tuomilehto, J. Feasibility of community programme for control of hypertension. A part of the North Karelia Project. Publications of the University of Kuopio. Community Health-series A-2/1975.
4. Tuomilehto, J., Puska, P. & Nissinen, A. Hypertension programme of the North Karelia Project. *Scand. J. soc. Med.* 4:67 1976.
5. Tuomilehto, J., Rajala, A.-L., & Puska, P. A study on the drop-outs of the hypertension register of the North Karelia Project. *Comm. Health* 7:149 1976.
6. Veterans Administration Study Group on Anti-hypertensive Agents: Effects of treatment on morbidity in hypertension. Results in patients with diastolic blood pressures averaging 115 through 129 mmHg. *J. Amer. med. Ass.* 202:1028 1967.
7. Veterans Administration Study Group on Anti-hypertensive Agents: Effects of treatment on morbidity in hypertension. II. Results in patients with diastolic blood pressures averaging 90 through 114 mmHg. *J. Amer. med. Ass.* 213:1143 1970.
8. World Health Organization: Community control of stroke and hypertension. Report of WHO meeting. *CVD* 72:1 1971.



## **Discussion.**

### *Berglund.*

One of the most important things you showed is that it is possible in the primary health service to treat a hypertensive population with acceptable control of blood pressure and with acceptable frequency of drop-outs

### *Tuomilehto.*

The public health nurses have done most of the check up visits and the results show what public health nurses can do. The efforts of the doctors were more or less the same as before our intervention.

### *Leren.*

Which drugs did you use and did the nurses have the right to prescribe antihypertensives?

### *Tuomilehto*

In Finland we have approximately 40 different antihypertensive drugs and I would guess that almost all of them have been used. About 70% of those treated get some kind of diuretic, about 50% some kind of beta blocker and some 30% methyldopa.

### *Puska*

The doctors prescribe the drugs but the nurses can regulate the treatment in close contact with the doctor. It is up to the local doctors to decide when to start the drug treatment.

# Coronary Risk and Socio-economic Status, The Oslo Study

P. LEREN, A. HELGELAND, I. HJERMANN, I. HOLME, and P.O. LUND-LARSEN  
From the Medical Out-Patient Clinic and Life Insurance Companies'  
Institute for Medical Statistics, Ullevål Hospital, Oslo, Norway

In the Oslo Study 18,000 men, aged 20-49 had a health examination. This examination, the screening phase, lasted from May 1972 to December 1973. The screening data were then matched with the 1970 census and the 1972 income data. The census data included information about the educational level of the participating men.

Detailed reports have earlier been published (1, 2, 3).

This presentation deals with 14,677 men aged 40-49 without known cardiovascular disease.

Blood pressure was independent of income. Increasing educational level, however, was associated with decreasing blood pressure. When the men were divided into five social classes taking into account both income and education certain characteristics proved to be dependent on the socio-economic level of the men.

Blood pressure showed a slight increase with decreasing socio-economic status. Serum cholesterol and percentage of daily smokers showed a marked and systematic increase from the highest to the lowest social class. Thus, the total coronary risk (risk score) based on systolic blood pressure, serum cholesterol and number of cigarettes increased from 5.7 in the highest social class to 13.3 in the lowest.

The study also revealed that various occupations were associated with different coronary risk. The four highest risk occupations were taxi drivers, construction workers and navvies, longshoremen and ship officers. The highest systolic pressure was recorded in metal foundry workers (140.8 mmHg) and the highest diastolic in ship officers (82.2 mmHg).

The four lowest risk occupations were

religious workers, physicians, lawyers and headmasters. The latter had both the lowest systolic and diastolic pressure (127.0/82.2 mmHg). Owing to small numbers in each occupational group a possible selection effect must be considered.

Dividing social class III into three subgroups, those with high income and low education (over-achievers), those with both medium income and education (medium-achievers) and those with low income and high education (under-achievers), a great variance in coronary risk emerged. Blood pressure and serum cholesterol showed significantly lower levels in the under-achievers, as compared with the over-achievers, and although cigarette smoking was very much the same, the total coronary risk rose from 8.2 in the under-achievers to 12.1 in the over-achievers.

Thus, coronary heart disease risk as judged from systolic blood pressure, serum cholesterol and number of cigarettes, seems to be linked to socio-economic status. Those with the highest educational and economic status are better off.

## References

1. Holme, I., Helgeland, A., Hjermann, I., Leren, P. & Lund-Larsen, P.O.: Coronary risk factors in various occupational groups. The Oslo Study. *Brit. J. prevent. soc. Med.* 31:96, 1977.
2. Holme, I., Helgeland, A., Hjermann, I., Lund-Larsen, P.O., & Leren, P.: Coronary risk factors and socioeconomic status. The Oslo Study. *Lancet* II, 1976, 1976.
3. Leren, P., Akeevold, E.M., Fosb, O., Frøth, A., Grynner, D., Helgeland, A., Hjermann, I., Holme, I., Lund-Larsen, P.O., & Norum, K.R.: The Oslo Study. Cardiovascular disease in middle-aged and young Oslo men. *Acta med scand. Suppl.* 588, 1975.

## **Discussion.**

### *Berglund*

One of the most important things you showed is that it is possible in the primary health service to treat a hypertensive population with acceptable control of blood pressure and with acceptable frequency of drop-outs

### *Tuomilehto*

The public health nurses have done most of the check-up visits and the results show what public health nurses can do. The efforts of the doctors were more or less the same as before our intervention

### *Leren.*

Which drugs did you use and did the nurses have the right to prescribe antihypertensives?

### *Tuomilehto.*

In Finland we have approximately 40 different antihypertensive drugs and I would guess that almost all of them have been used. About 70% of those treated get some kind of diuretic, about 50% some kind of beta-blocker and some 30% methyldopa

### *Puska*

The doctors prescribe the drugs but the nurses can regulate the treatment in close contact with the doctor. It is up to the local doctors to decide when to start the drug treatment

# Coronary Risk and Socio-economic Status, The Oslo Study

P. LEREN, A. HELGELAND, L. HJERMANN, I. HOLME, and P.O. LUND-LARSEN  
From the Medical Out-Patient Clinic and Life Insurance Companies  
Institute for Medical Statistics, Ullevål Hospital, Oslo, Norway

In the Oslo Study 18,000 men aged 20-49 had a health examination. This examination, the screening phase, lasted from May 1972 to December 1973. The screening data were then matched with the 1970 census and the 1972 income data. The census data included information about the educational level of the participating men.

Detailed reports have earlier been published (1, 2, 3).

This presentation deals with 14,677 men aged 40-49 without known cardiovascular disease.

Blood pressure was independent of income. Increasing educational level, however, was associated with decreasing blood pressure. When the men were divided into five social classes taking into account both income and education certain characteristics proved to be dependent on the socio-economic level of the men.

Blood pressure showed a slight increase with decreasing socio-economic status. Serum cholesterol and percentage of daily smokers showed a marked and systematic decrease from the highest to the lowest social class. Thus, the total coronary risk (risk score) based on systolic blood pressure, serum cholesterol and number of cigarettes, increased from 5.7 in the highest social class to 13.3 in the lowest.

The study also revealed that various occupations were associated with different coronary risk. The four highest risk occupations were taxi drivers, construction workers and navvies, longshoremen and ship's officers. The highest systolic pressure was measured in metal foundry workers (140.8 mmHg) and the highest diastolic in ship's officers (82.2 mmHg).

The four lowest risk occupations were

religious workers, physicians, lawyers and headmasters. The latter had both the lowest systolic and diastolic pressure (127.0/82.2 mmHg). Owing to small numbers in each occupational group a possible selection effect must be considered.

Dividing social class III into three subgroups, those with high income and low education (over-achievers), those with both medium income and education (medium-achievers), and those with low income and high education (under-achievers), a great variance in coronary risk emerged. Blood pressure and serum cholesterol showed significantly lower levels in the under-achievers, as compared with the over-achievers, and although cigarette smoking was very much the same, the total coronary risk rose from 8.2 in the under-achievers to 12.1 in the over-achievers.

Thus coronary heart disease risk as judged from systolic blood pressure, serum cholesterol, and number of cigarettes, seems to be linked to socio-economic status. Those with the highest educational and economic status are better off.

## References

1. Holme, I., Helgeland, A., Hjermann, L., Leren, P. & Lund-Larsen, P.O. Coronary risk factors in various occupational groups. The Oslo Study. *Brit. J. Prev. Soc. Med.* 31:96, 1977.
2. Holme, I., Helgeland, A., Hjermann, L., Lund-Larsen, P.O. & Leren, P. Coronary risk factors and socioeconomic status. The Oslo Study. *Lancet* II, 1396, 1976.
3. Leren, P., Askevold, E.M., Fos, O., Frølich, A., Grynø, D., Helgeland, A., Hjermann, L., Holme, I., Lund-Larsen, P.O., & Norum, K.R. The Oslo Study. Cardiovascular disease in middle-aged and young Oslo men. *Acta med. scand., Suppl.* 582, 1975.

## Discussion

### *Berglund*

One of the most important things you showed is that it is possible in the primary health service to treat a hypertensive population with acceptable control of blood pressure and with acceptable frequency of drop-outs

### *Tuomilehto*

The public health nurses have done most of the check-up visits, and the results show what public health nurses can do. The efforts of the doctors were more or less the same as before our intervention

### *Leren*

Which drugs did you use and did the nurses have the right to prescribe antihypertensives?

### *Tuomilehto*

In Finland we have approximately 40 different antihypertensive drugs and I would guess that almost all of them have been used. About 70% of those treated get some kind of diuretic, about 50% some kind of beta-blocker and some 30% methyldopa.

### *Puska*

The doctors prescribe the drugs but the nurses can regulate the treatment in close contact with the doctor. It is up to the local doctors to decide when to start the drug treatment.

Extra follow-up visits:	Nkr	72,000
Additional laboratory analyses:	Nkr	88,000
Income loss (2 working hours per visit):	Nkr	144,000
Antihypertensive drugs:	Nkr	860,000
	Nkr	1164,000

*Additional cost per patient per year*  
Nkr 730

If the treatment cut off point is reduced from diast. 110 to 100 mmHg, additional 40-50,000 Norwegians will have to be treated with antihypertensive drugs (7). Thus an uncertain health gain will cost another 36 million Nkr per year compared to a non-drug regimen with systematic follow-up. This calculation does not include the cost of possible side effects of the drug.

2. *The side-effects of the drugs* observed in this trial are about the same as seen in other studies. We have also looked for possible effects of thiazides on serum lipids. In the total group treated with thiazides there was no significant increase in serum triglycerides and cholesterol was unchanged. In those who experienced the greatest increase in uric acid during thiazide treatment, there was a significant increase in triglycerides. Cholesterol was unchanged. Increase in body weight during thiazide treatment seems to induce a significantly greater increase in serum uric acid and triglycerides than corresponding weight increase in the control group (2).

3. *The drop-out problem* in the treatment of mild hypertension seems to vary in different populations, and with different ways of managing the follow-up examinations (1-4). In this study the patients have seen the same physician and the same paramedical staff during 4 years and the drop-out rate has been small, 0.6 per cent, and the same in both groups, (Table I).

4. *Does drug regimen lead to more mental anxiety than a non-drug observation routine?*

Table II shows preliminary results from a

Table I. Oslo Study Drop-outs from hypertension trial.

Total number of observed patients in the treatment and control group		785
4 years observation.		
Drop-out rate	0.6 per cent	
Treatment group	2 patients	
Control group	3 patients	

questionnaire mailed to both groups. Only few patients equal in both groups, reported that the procedure had promoted a feeling of anxiety.

Only about 10 per cent of the patients would have preferred the follow-up to have taken place in their private physician's surgery.

Table II. Oslo Study Condition of patients.

Regimen	Feeling of anxiety	Feeling of safety	Indifferent
Drug treatment (n=80)	2.5%	80*	17.5%
No drug treatment and follow-up visits (n=100)	1%	86%	13*

The blood pressure difference between the two regimens is 17 mmHg systolic and about 10 mmHg diastolic. About 8 per cent of the control group have passed the "ethical roof" with blood pressure above 180/110 mmHg (mean of the two lowest readings of 3 visits 3 weeks apart). These patients have been offered treatment. Reports of cardiovascular events will be presented in 1979 when all patients have been in the trial for at least 5 years.

#### References

1. Caldwell, J.R., Cobb, S., Dowling, M.D. & De Jough, D. The drop-out problem in antihypertensive treatment. *J. Chron. Dis.* 22: 579 1970.
2. Hjeltnes, A., Hjeltnes, L., Holm, L. & Leren, P. Serum triglycerides and serum uric acid in untreated and thiazide treated mild hypertension. *Am. J. Med.* 64:34, 1978.

# Mild Hypertension - Early Drug Treatment or Follow-up only? The Oslo Study

A. HELGELAND, I. BAKSAAS AASEN and P. LEREN

From the Medical Out Patient Clinic and Division of Clinical Pharmacology and Toxicology, Central Laboratory, Ullevaal Hospital, Oslo, Norway

The 1970 Veterans Administration report of drug treatment of mild and moderate hypertension (diastolic BP 90-114 mmHg) aroused great interest in hypertension treatment (5). Later reports from the same centre have shown fewer benefits from drug treatment of milder hypertension (diastolic BP 90-104 mmHg) unless the patients had cardiovascular complications at entry or were above 50 years of age (6). It seems that persons with mild hypertension without complications are at a lower risk and possible benefits from drug treatment should be weighed against the inconvenience, side effects and cost of drug treatment. From their controlled trial of drug treatment of mild hypertension in 400 patients for 10 years, McFate Smith et al. conclude that a non-drug regimen with systematic follow-up may be a useful alternative to drug treatment (3).

The hypertension trial in the Oslo Study started in 1973 with 406 men in the drug group and 379 men in a non-treated control group (no placebo). Age at start was 40-49 and blood pressure range was 150-179 mmHg systolic, and below 110 mmHg diastolic. Sample size is small and a 5 year follow up study might not be conclusive with regard to "hard" events such as death, myocardial infarction and cerebrovascular accidents. Additional information might be gained by exercise tests at start and at 5-year follow-up. Another aim is to gain practical experience with the management of symptom-free hypertensives and to elucidate side effects of the antihypertensive drugs.

Some experiences from 4-year follow up will be discussed.

*1. Additional cost of drug regimen compared with a non-drug management with systematic follow-up*

The calculations were based on experiences from pretreatment examinations, average drug doses and other follow-up results. Analyses made for pure, scientific reasons have been omitted.

*The drug regimen.* Hydrochlorothiazide 50 mg per day. If blood pressure remains above 140/90 mmHg, alpha-methyldopa has been added. In case of side effects, alpha-methyldopa has been replaced by propranolol. At 4-year follow-up the distribution of the drugs was: Hydrochlorothiazide (HCTH) alone: 190 patients; HCTH + alpha-methyldopa: 89; HCTH + propranolol: 92; other drugs: 33. Two patients refused to take drugs.

Pretreatment evaluation was the same in both groups.

After start the treated patients had 4 follow-up visits the first year, later 2 visits each year. The control patients have been seen once a year.

*Laboratory tests.* Serum potassium and uric acid have been done after 3 months in the treatment group, later once a year, fasting blood glucose after 3 years. These analyses have not been undertaken in the control group. All other tests have been equal for the two groups.

*Additional costs.* In the treatment group compared with the controls during 4 years (400 patients):

Extra follow-up visits:	Nkr	72,000
Additional laboratory analyses:	Nkr	88,000
Income loss (2 working hours per visit):	Nkr	144,000
Antihypertensive drugs:	Nkr	860,000
	Nkr	1164,000

Additional cost per patient per year

Nkr 730

If the treatment cut off point is reduced from diast. 110 to 100 mmHg, additional 40-50,000 Norwegians will have to be treated with antihypertensive drugs (7). Thus an uncertain health gain will cost another 36 million Nkr per year compared to a non-drug regimen with systematic follow-up. This calculation does not include the cost of possible side effects of the drug.

2. *The side-effects of the drugs* observed in this trial are about the same as seen in other studies. We have also looked for possible effects of thiazides on serum lipids. In the total group treated with thiazides there was no significant increase in serum triglycerides, and cholesterol was unchanged. In those who experienced the greatest increase in uric acid during this side treatment, there was a significant increase in triglycerides. Cholesterol was unchanged. Increase in body weight during thiazide treatment seems to induce a significantly greater increase in serum uric acid and triglycerides than corresponding weight increase in the control group (2).

3. *The drop-out problem* in the treatment of mild hypertension seems to vary in different populations, and with different ways of managing the follow-up examinations (1-4). In this study the patients have seen the same physician and the same paramedical staff during 4 years and the drop-out rate has been small, 0.6 per cent, and the same in both groups, (Table I).

4. *Does a drug regimen lead to more mental anxiety than a non-drug observation routine?*

Table II shows preliminary results from a

Table I Oslo Study Drop-outs from hypertension trial.

Total number of observed patients in the treatment and control group		
4 years observation		785
Drop-out rate	0.6 per cent	
Treatment group	2 patients	
Control group	3 patients	

questionnaire mailed to both groups. Only few patients, equal in both groups, reported that the procedure had promoted a feeling of anxiety.

Only about 10 per cent of the patients would have preferred the follow-up to have taken place in their private physician's surgery.

Table II Oslo Study Condition of patients.

Regimen	Feeling of anxiety	Feeling of safety	Indif- ferent
Drug treatment (n = 80)	2.5%	80%	17.5%
No drug treatment and follow-up visits (n = 100)	1%	86%	13%

The blood pressure difference between the two regimens is 17 mmHg systolic and about 10 mmHg diastolic. About 8 per cent of the control group have passed the "ethical roof" with blood pressure above 180/110 mmHg (mean of the two lowest readings of 3 visits 3 weeks apart). These patients have been offered treatment. Reports of cardiovascular events will be presented in 1979 when all patients have been in the trial for at least 5 years.

#### References

1. Caldwell, J.R., Cobb, E., Dowling, M.D. & De Jongh, D.: The drop-out problem in antihypertensive treatment. *J. Chron. Dis.* 22: 579 1970.
2. Hjeltnad, A., Hjertqvist, I., Hobos, I. & Leren, W.: Serum triglycerides and serum uric acid in untreated and thiazide treated mild hypertension. *Am. J. Med.* 64:34, 1978.



# Mild Hypertension - Early Drug Treatment or Follow-up only? The Oslo Study

A HELGELAND I BAKSAAS AASEN and P LEREN

From the Medical Out Patient Clinic and Division of Clinical Pharmacology and Toxicology Central Laboratory Ullevaal Hospital, Oslo, Norway

The 1970 Veterans Administration report of drug treatment of mild and moderate hypertension (diastolic BP 90-114 mmHg) aroused great interest in hypertension treatment (5). Later reports from the same centre have shown fewer benefits from drug treatment of milder hypertension (diastolic BP 90-104 mmHg) unless the patients had cardiovascular complications at entry or were above 50 years of age (6). It seems that persons with mild hypertension without complications are at a lower risk and possible benefits from drug treatment should be weighed against the inconvenience side effects and cost of drug treatment. From their controlled trial of drug treatment of mild hypertension in 400 patients for 10 years McFate Smith et al. conclude that a non-drug regimen with systematic follow-up may be a useful alternative to drug treatment (3).

The hypertension trial in the Oslo Study started in 1973 with 406 men in the drug group and 379 men in a non-treated control group (no placebo). Age at start was 40-49 and blood pressure range was 150-179 mmHg systolic, and below 110 mmHg diastolic. Sample size is small and a 5 year follow-up study might not be conclusive with regard to "hard" events such as death, myocardial infarction and cerebrovascular accidents. Additional information might be gained by exercise tests at start and at 5-year follow-up. Another aim is to gain practical experience with the management of symptom free hypertensives and to elucidate side effects of the antihypertensive drugs.

Some experiences from 4-year follow-up will be discussed.

*1 Additional cost of drug regimen compared with a non-drug management with systematic follow up*

The calculations were based on experiences from pretreatment examinations, average drug doses and other follow-up results. Analyses made for pure scientific reasons have been omitted.

*The drug regimen.* Hydrochlorothiazide 50 mg per day. If blood pressure remains above 140/90 mmHg, alpha-methyldopa has been added. In case of side effects alpha-methyldopa has been replaced by propranolol. At 4-year follow-up the distribution of the drugs was: Hydrochlorothiazide (HCTH) alone: 190 patients. HCTH + alpha methyldopa: 89. HCTH + propranolol: 92. Other drugs: 33. Two patients refused to take drugs.

Pretreatment evaluation was the same in both groups.

After start the treated patients had 4 follow-up visits the first year, later 2 visits each year. The control patients have been seen once a year.

*Laboratory tests.* Serum potassium and uric acid have been done after 3 months in the treatment group, later once a year, fasting blood glucose after 3 years. These analyses have not been undertaken in the control group. All other tests have been equal for the two groups.

*Additional costs in the treatment group compared with the controls during 4 years (400 patients)*

# Prevalence of Hypertension in the Glostrup Population Studies

LEIF HAGERUP, MARIANNE SCHROLL, MARIE ERIKSEN, HANNE HOLLNAGEL, and ERIK AGNER

From the Section of Prospective Medicine, Medical Department C, Glostrup County Hospital, Copenhagen, Denmark

The Glostrup population studies are prospective studies of 40, 50, 60, 70 and 80 year old men and women.

From the communities surrounding Glostrup Hospital the total populations from each decade have been invited to an examination. Each separate survey was primarily aimed at investigating the prevalence of cardiovascular risk factors. The surveys of the 60 and 80 year old people furthermore serve as incidence studies as they are re-examinations of the 50 and 70 year old populations previously studied.

The examination program included questionnaires, physical examination, chest X-ray, ECG at rest and during exercise and blood samples, according to criteria of WHO.

The blood pressure was measured after 10 minutes rest in the supine position with a standard cuff and a mercury manometer. The diastolic blood pressure was measured at the disappearance of the Korotkoff sounds (phase V).

Table I. Systolic BP  $\pm$  sd/Diastolic BP  $\pm$  sd in men

40 years old.	125 $\pm$ 17 / 81 $\pm$ 11	(n = 500)
50 years old.	137 $\pm$ 19 / 87 $\pm$ 13	(n = 431)
60 years old.	138 $\pm$ 22 / 87 $\pm$ 13	(n = 359)
70 years old.	153 $\pm$ 23 / 86 $\pm$ 13	(n = 223)
80 years old.	137 $\pm$ 22 / 71 $\pm$ 13	(n = 99)

Table II. Systolic BP  $\pm$  sd/Diastolic BP  $\pm$  sd in women

40 years old.	118 $\pm$ 15 / 75 $\pm$ 10	(n = 528)
50 years old.	141 $\pm$ 22 / 87 $\pm$ 13	(n = 355)
60 years old.	140 $\pm$ 24 / 86 $\pm$ 14	(n = 306)
70 years old.	157 $\pm$ 28 / 82 $\pm$ 13	(n = 206)
80 years old.	147 $\pm$ 26 / 70 $\pm$ 12	(n = 130)

Tables I and II show as in other studies increasing systolic blood pressure with age, especially in women past 50.

Frequency of treatment with antihypertensive drugs varied from 0.3% of the 50 year old population to 6.8% of the 60 year old, whereas diuretics were used by 1.5% of the 50 year old, by 11.6% of the 80 year old men and by 40% of the 80 year old women.

A great part of those treated did not achieve sufficient lowering of the blood pressure which means that the found prevalence figures are not far from real values.

Using limits proposed by WHO for hypertension (systolic BP  $\geq$  160 and diastolic BP  $\geq$  95) treatment will be needed in the proportion of each age group shown in table III.

Table III. Proportion of each age group needing antihypertensive therapy

Men	Women
40 year old: 11/300 = 3.7%	8/528 = 1.5%
50 year old: 45/436 = 10%	51/360 = 14%
60 year old: 40/359 = 11%	37/306 = 12%
70 year old: 30/223 = 13%	33/206 = 16%
80 year old: 4/99 = 4%	4/130 = 3%

In the 10 year follow-up of the original 50 year old population it was found that the incidence of cardiovascular diseases was related to increasing diastolic blood pressure and especially to diastolic pressures over 100 mmHg. Though the blood pressure was only measured on one occasion it seemed to be a good predictor of future risk.

## References

1. Hagerup, L.M.: Coronary heart disease risk

3. M. Tarkenton, W. Edlward, S.A., Brumer, L. & Mark Kravitz, W. Mortality and morbidity in mild hypertension: 1953 Hospital intervention trial. CVD Epidemiology Newsletters (American Heart Association) 12: 22 1971.
4. Scander, R., Scander, J., Connell, J., Pritchard, D., Gorch, F.C., Tisho, S., Levine, B. & Fine, D., Adherence and blood pressure response to hypertension treatment. *Lancet* 2, 1971 1971.
5. Veterans Administration Study Group on Antihypertensive Agents: Effects of treatment on morbidity in hypertension. II. Results in patients with diastolic blood pressure averaging 97 through 114 mm.Hg. *J. Am. med. Ass.* 212: 1962, 1971.
6. Veterans Administration Study Group on Antihypertensive Agents: Effects of treatment on morbidity in hypertension. III. Influence of Age, diastolic pressure and prior cardiovascular disease, further analysis of side effects. *Circulation* 42: 971, 1971.
7. Wadler, Hans "L". Personal communication.

## Discussion:

### After

How has the blood pressure development been in the untreated control group.

Ans. Furthermore, has there ever been a proper investigation on what happens to high blood pressure when the medicine is discontinued?

### Helpless:

In our untreated control group the mean blood pressure level is surprisingly steady from year to year, but in about 20 percent of the patients there seems to place a distinct increase in blood pressure.

### Reckless:

I have also felt that this is a very important question and one which I have considered during my long term observations. My impression is that of course the main group lies at a certain level, but there are many exceptions. For example, some patients, some regain their normal blood pressure, or at any rate a lower blood pressure, and so it is quite certain that the same level can be maintained without using 4 or more years. However, a slight increase during the years is most common.

### How Often:

In the Veterans Administration study there was an observation period of about 4 years for both the placebo group and the treatment group. In the placebo group, there were quite a few whose diastolic blood pressure rose during that period and who definitely needed treatment. The active treatment was discontinued in a large number. A month or two might pass, but at some time after withdrawal the blood pressure rose in most of the patients to levels again requiring hypertensive treatment.

# Prevalence of Hypertension in the Glostrup Population Studies

LEIF HAGERUP, MARIANNE SCHROLL, MARIE ERIKSEN, HANNE HOLLNAGEL, and ERIK AGNER

From the Section of Prospective Medicine, Medical Department C, Glostrup County Hospital, Copenhagen, Denmark

The Glostrup population studies are prospective studies of 40, 50, 60, 70 and 80 year old men and women.

From the communities surrounding Glostrup Hospital the total populations from each decade have been invited to an examination. Each separate survey was primarily aimed at investigating the prevalence of cardiovascular risk factors. The surveys of the 60 and 80 year old people furthermore serve as incidence studies as they are re-examinations of the 50 and 70 year old populations previously studied.

The examination program included questionnaires, physical examination, chest X-ray, ECG at rest and during exercise and blood samples, according to criteria of WHO.

The blood pressure was measured after 10 minutes' rest in the supine position with a standard cuff and a mercury manometer. The diastolic blood pressure was measured at the disappearance of the Korotkoff sounds (phase V).

Table I. Systolic BP  $\pm$  sd/Diastolic BP  $\pm$  sd in men

40 years old.	125 $\pm$ 17 / 81 $\pm$ 11	(n = 500)
50 years old.	137 $\pm$ 19 / 87 $\pm$ 13	(n = 431)
60 years old.	138 $\pm$ 22 / 87 $\pm$ 13	(n = 359)
70 years old.	153 $\pm$ 23 / 86 $\pm$ 13	(n = 223)
80 years old.	137 $\pm$ 22 / 71 $\pm$ 13	(n = 99)

Table II. Systolic BP  $\pm$  sd/Diastolic BP  $\pm$  sd in women

40 years old:	118 $\pm$ 15 / 75 $\pm$ 10	(n = 528)
50 years old.	141 $\pm$ 22 / 87 $\pm$ 13	(n = 355)
60 years old.	140 $\pm$ 24 / 86 $\pm$ 14	(n = 306)
70 years old.	157 $\pm$ 28 / 82 $\pm$ 13	(n = 206)
80 years old.	147 $\pm$ 26 / 70 $\pm$ 12	(n = 130)

Tables I and II show as in other studies increasing systolic blood pressure with age especially in women past 50.

Frequency of treatment with antihypertensive drugs varied from 0.3% of the 50 year old population to 6.8% of the 60 year old, whereas diuretics were used by 1.5% of the 50 year old, by 11.6% of the 80 year old men, and by 40% of the 80 year old women.

A great part of those treated did not achieve sufficient lowering of the blood pressure, which means that the found prevalence figures are not far from real values.

Using limits proposed by WHO for hypertension (systolic BP  $\geq$  160 and diastolic BP  $\geq$  95), treatment will be needed in the proportion of each age group shown in table III.

Table III. Proportion of each age group needing antihypertensive therapy

	Men	Women
40 year old.	11/500 = 2.2%	8/528 = 1.5%
50 year old.	45/434 = 10%	51/360 = 14%
60 year old.	40/359 = 11%	37/306 = 12%
70 year old.	50/223 = 22%	35/206 = 17%
80 year old.	4/99 = 4%	4/130 = 3%

In the 10 year follow-up of the original 50 year old population it was found that the incidence of cardiovascular diseases was related to increasing diastolic blood pressure and especially to diastolic pressures over 100 mmHg. Though the blood pressure was only measured on one occasion it seemed to be a good predictor of future risk.

## References

1. Hagerup, L.M.: Coronary heart disease risk

3. Mc Fie Smith, W., Edlvaugh, S. A., Brown, L. & Mark Krasner, W., "Morbidity and mortality in mild hypertension: FHS Hospital intervention trial." *CVD Epidemiology Newsletter*, American Heart Association, 12: 25, 1971.
4. Smoller, T., Smoller, J., Cynell, J., Puchner, D., Goss, F. C., Tolin, S., Farrow, B. & Fine, D., "Adherence and blood pressure response to hypertensive treatment." *Lancet*, 1: 1007, 1971.
5. Veterans Administration Study Group in Antihypertensive Agents: "Effect of treatment on morbidity in hypertension. III. Results in patients with diastolic blood pressure averaging 97 through 114 mmHg." *J. Am. med. Ass.* 224: 1163, 1970.
6. Veterans Administration Study Group in Antihypertensive Agents: "Effect of treatment on morbidity in hypertension. III. Influence of Age, diastolic pressure and prior cardiovascular disease: further analysis of data of first Cardiovascular 45: 492, 1971.
7. Winkler, Hans Th., *Personal communication*.

## Discussion:

### Age:

First, how the blood pressure development "seen in the untreated control group."

And "indeed, has there ever been a proper investigation on what happens to high blood pressure when the medicine is discontinued?"

### Geipeland:

In our untreated control group the mean blood pressure level is surprisingly stable from year to year, but in about 10-20 percent of the patients there seems to take place a distinct increase in blood pressure.

### Sechgaard:

I have also felt that this is a very important question and one which I have considered during my long term observations. My impression is that of course the mean group lies at a certain level, but there are many exceptions. For metabolic reasons, some regain their normal blood pressure, or at any rate a lower blood pressure, just as it is just certain that the same level can be maintained without using for many years. However, a slight increase during the years is most common.

### Sten "Lars:

In the Veterans Administration study there was an observation period of about 4 years for both the placebo group and the treatment group. In the placebo group, there were quite a few whose diastolic blood pressure rose during that period and who definitely needed treatment. The active treatment was discontinued in a hypertension. A month or two might pass, but at some time after withdrawal the blood pressure rose in most of the patients to levels again requiring hypertensive treatment.

# Cardiovascular Manifestations and Changes in Blood Pressure from the Age of 50 to the Age of 60, in the Glostrup Population of Men and Women Born in 1914

MARIANNE SCHROLL

From the Section of Prospective Medicine, Medical Dept. C, Glostrup County Hospital, Copenhagen, Denmark

In 1964 a total population of 514 men and 461 women, living in seven municipalities around Glostrup County Hospital, was invited for a health examination with special emphasis on risk factors for coronary heart disease. Eighty-two per cent of the 975 proposals participated in the baseline-examination. After a ten year interval the 790 survivors were invited for a follow-up examination in which 666 participated. On both occasions blood pressure was measured several times. For comparison we used the 10 o'clock supine blood pressure taken after 10 minutes' rest (using Korotkoff phase V as diastolic blood pressure).

No statistically significant difference was found between the distribution curves of systolic or diastolic blood pressure measured at the age of fifty and the age of sixty (1). This does not imply that the incidence of hypertension was zero. In this survey hypertensives had a considerable mortality. Anti-hypertensive drugs lowered the blood pressure in some of the participants treated by their general practitioners. Non-participants and participants in the re-examination did not differ in entry blood pressure values. Some participants must then have developed hypertension over the decade. It is of some importance to know if it was the borderline-hypertensives who developed manifest hypertension.

The target population was the participants who had a blood pressure registered in 1964 when they were 50 and in 1974 when they were 60. For those 627 participants a straight correlation (with  $y = x$ ) was found between systolic blood pressure

at the age of 50 ( $SBP_{50}$ ) and  $SBP_{60}$ . A well marked scattering was observed ( $r = 0.54$ ).

In Figs. 1 and 2 participants undergoing hypertensive treatment during the period 1964 to 1974 were excluded. According to systolic blood pressure at the age of 50 the participants were divided in deciles. In Fig. 1 the same participants were divided in deciles according to  $SBP_{60}$  illustrating the spontaneous change in blood pressure during the decade. The highest decile of the participants in the baseline examination had  $SBP \geq 165$  mmHg and might be regarded a "high risk group". Fig. 2 shows that only 13 participants from this group at the age of 60 still belonged to the highest decile. Twenty probands had drifted towards lower blood pressure values. Simultaneously 58 individuals from the "low risk group" in 1964 progressed to the highest decile in 1974. We ought to have kept the 9th decile (baseline blood pressures from 155-160 mmHg) under observation, expecting hypertensives to emerge from this group over time. Thirteen did so. 8 stayed in the 9th decile, while 24 obtained normal blood pressures. At the same time 39 individuals moved up into the borderline-decile.

The group belonging to the highest decile at the age of 50, had a considerable overmortality and overmorbidity 1964-1974. Fifty-six men had  $SBP_{50} \geq 160$  mmHg. The ten-year mortality in this group was 29% compared to 11% among the 375 men in "the low risk group". The incidence of cardiovascular manifestations (fatal and nonfatal) was 33% in "the high

factors in men and women. Acta med scand. suppl. 557 1974

2. Raeder R. Screening methods in community control of hypertension. In: Pathophysiology and management of arterial hypertension (ed. O. Berghund et al.) Copenhagen 1975
3. Schroll, M. & Hagerup L.M. Risk factors of myocardial infarction in men aged fifty at entry Danish med Bull 1977 24 252 255

## Discussion

### *Ager*

The low frequency in 80 year olds may be connected with the fact that patients with hypertension have had some other disease myocardial infarction or something else, which results in a lower blood pressure.

# Cardiovascular Manifestations and Changes in Blood Pressure from the Age of 50 to the Age of 60, in the Glostrup Population of Men and Women Born in 1914

MARIANNE SCHROLL

From the Section of Prospective Medicine, Medical Dept. C, Glostrup County Hospital, Copenhagen, Denmark

In 1964 a total population of 514 men and 461 women, living in seven municipalities around Glostrup County Hospital was invited for a health examination with special emphasis on risk factors for coronary heart disease. Eighty-two per cent of the 975 *proposita* participated in the baseline-examination. After a ten year interval the 790 survivors were invited for a follow-up examination in which 666 participated. On both occasions blood pressure was measured several times. For comparison we used the 10 o'clock saphire blood pressure taken after 10 minutes rest (using Korotkoff phase V as diastolic blood pressure).

No statistically significant difference was found between the distribution curves of systolic or diastolic blood pressure measured at the age of fifty and the age of sixty (1). This does not imply that the incidence of hypertension was zero. In this survey hypertensives had a considerable mortality. Antihypertensive drugs lowered the blood pressure in some of the participants treated by their general practitioners. Non-participants and participants in the re-examination did not differ in entry blood pressure values. Some participants must then have developed hypertension over the decade. It is of some importance to know if it was the borderline-hypertensives who developed manifest hypertension.

The target population was the participants who had a blood pressure registered in 1964, when they were 50 and in 1974 when they were 60. For those 627 participants a straight correlation (with  $y = x$ ) was found between systolic blood pressure

at the age of 50 ( $SBP_{50}$ ) and  $SBP_{60}$ . A well-marked scattering was observed ( $r = 0.54$ ).

In Figs 1 and 2 participants undergoing hypertensive treatment during the period 1964 to 1974 were excluded. According to systolic blood pressure at the age of 50 the participants were divided in decenniles. In Fig. 1 the same participants were divided in decenniles according to  $SBP_{60}$  illustrating the spontaneous change in blood pressure during the decade. The highest decennile of the participants in the baseline examination had  $SBP > 165$  mmHg and might be regarded a "high risk group". Fig. 2 shows that only 13 participants from this group at the age of 60 still belonged to the highest decennile. Twenty probands had drifted towards lower blood pressure values. Simultaneously 58 individuals from the "low risk group" in 1964 progressed to the highest decennile in 1974. We ought to have kept the 9th decennile (baseline blood pressures from 155-160 mmHg) under observation, expecting hypertensives to emerge from this group over time. Thirteen did so: 8 stayed in the 9th decennile, while 24 obtained normal blood pressures. At the same time 39 individuals moved up into the borderline-decennile.

The group belonging to the highest decennile at the age of 50, had a considerable overmortality and overmorbidity 1964-1974. Fifty-six men had  $SBP_{50} > 160$  mmHg. The ten-year mortality in this group was 29% compared to 11% among the 375 men in "the low risk group". The incidence of cardiovascular manifestations (fatal and nonfatal) was 35% in "the high



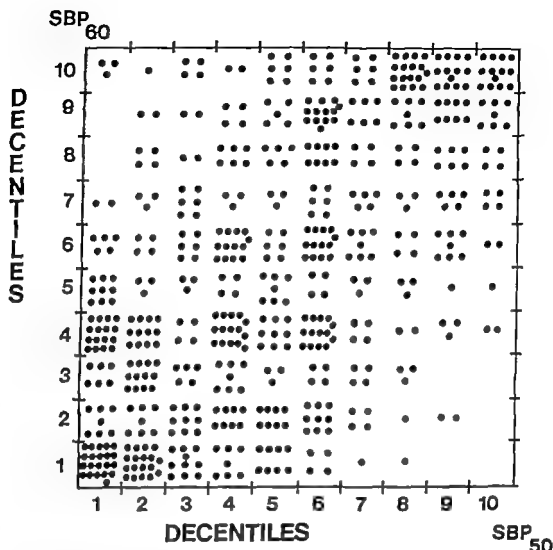


Fig 1 Systolic blood pressure in deciles aged 50 and 60 from the Glostrup population studies of men and women born in 1914. Participants undergoing hypertensive treatment during the period 1964-74 are excluded.

risk group" and 9% in "the low risk group". At the re-examination in 1974 20-30% of the men with high entry blood pressures had angina pectoris, intermittent claudication and dyspnoea on exercise in contrast to 4-9% of the rest. There was an overrepresentation (but not statistically significant) over hypertensive organ-changes at age 60 among men with high blood pressures at entry.

The severe consequences of hypertension might be diminished by a transformation of the entire blood pressure distribution in the population towards lower values. A large scale weight reduction and improvement of physical fitness might influ-

ence the blood pressure distribution in a population, but this is still to be proved.

#### References

1. Hagerup, L., Schroll, M. & Ibsen, H. High blood pressure as a risk factor for cardiovascular disease, and risk factors for hypertension. From the Glostrup Population Studies. *Acta med. scand. Suppl. 602*, 1976.

#### Discussion.

*Poul Ebbe Nielsen.*

Is it possible that hypertension sometimes takes a cyclic course with patients passing through high blood pressure periods last

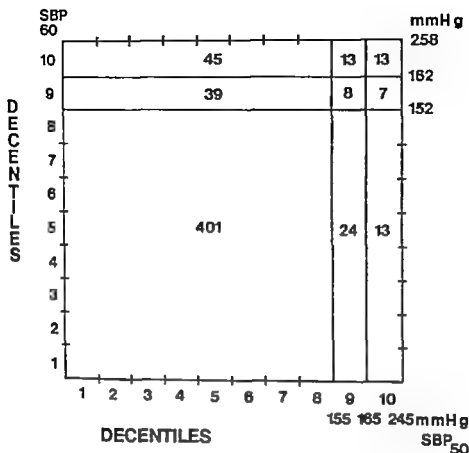


Fig 2 The spontaneous change from high risk to low risk groups and vice versa over 10-year period illustrated by separating the two highest SBP deciles in figure 1 at age 50 and 60.

lag months or perhaps years, after which the blood pressure again returns to normal without any form of treatment?

*Mariann Schroll.*

I have no observations supporting the theory of a cyclic course. However I think it would be interesting in our material to define a group which has not had raised blood pressure to see what characterizes it. So far, we have only concentrated on characterizing the high blood pressure group.

# The Prevalence of High Blood Pressure among 40 Year Old Men and Women

HANNE HOLLNAGEL, ARNE LETH HANS IBSEN and FINN KAMPER JØRGENSEN  
From the Section of Prospective Medicine Medical Department C,  
Glostrup County Hospital, Copenhagen, Denmark

The aim of this presentation was to elucidate the following two points

- 1 The prevalence of hypertension in a population of 40 year old men and women
- 2 Is screening for high blood pressure possible through the existing Danish health system?

A detailed description of the methods used in the Glostrup population studies has been published elsewhere (1, 2, 3). In the present study a population of 1199 persons born in 1936 and living in Glostrup and three neighbouring municipalities was selected. The group was assumed to be representative of the 40 year old men and women in Denmark. All were offered a health examination at the Section for Prospective Medicine and the overall response rate was 88%. Among the non-participating 12% 61% answered the questionnaire concerning health and occupation either by telephone or in writing. When attending the health examination measurement of blood pressure (BP) was carried out by one investigator (H.H.). The blood pressure measurements were standardized in accordance with the WHO recommendations (4) diastolic BP indicated as phase V (disappearance of the Korotkoff's sounds) using a mercury manometer (5).

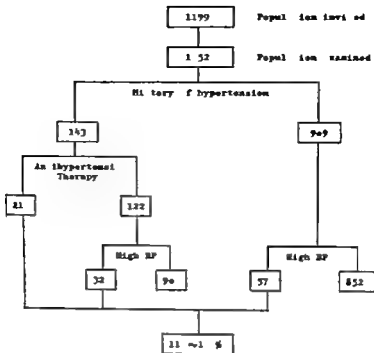
BP recordings were carried out in the morning after 5 minutes rest in the sitting position each value representing an average of two determinations. The criterion of hypertension was diastolic BP  $\geq 95$  mmHg in accordance with the WHO recommendation. Persons with high BP values were referred to the out-patient hypertension

clinic where the diagnosis of hypertension was ascertained by repeated ambulatory BP measurements and aetiological screening was carried out. Contacts with the existing Danish health system, i.e. general practitioners, hospitals, specialists and emergency wards were assessed by questionnaires.

The average casual BP in the population was  $124 \pm 14$  mmHg (mean  $\pm$  s.d.) systolic and  $82 \pm 11$  mmHg (mean  $\pm$  s.d.) diastolic. Women had significantly lower BP than men in accordance with earlier investigations. By application of the WHO criteria for hypertension high BP was demonstrated in 9.3% of the population, in a proportion of 3.1 in men and women.

Fig. 1 shows a flow diagram illustrating the 40 year old population divided according to history of hypertension, actual treatment and BP at the examination. Among 143 persons with a history of high BP 21 were on antihypertensive treatment and among the remaining 122 without treatment 32 still had raised BP. Among 909 persons without history of hypertension, 57 were found to have an increased BP. Thus a total of 110 persons had high BP i.e. 10% of the population studied. In accordance with earlier studies approximately 50% of the cases with high BP were hitherto unknown. Forty per cent of the cases with a history of high BP had never received antihypertensive therapy. In patients who had been treated for hypertension 30% had discontinued the therapy and only half of the cases on treatment were normotensive at the examination.

Until now 53 persons have attended the out-patient hypertension clinic with at least three visits and among these 21 (40%) had



BP Blood Pressure

Fig. 1 The 40 year population divided according to history of hypertension, actual treatment and increased blood pressure (diastolic  $\geq 95$  mmHg) at the examination day

a sustained diastolic BP in accordance with the diagnosis hypertension ( $\geq 95$  mmHg diastolic). Renovascular hypertension was not diagnosed in any case. In the population the BP has been previously measured in 88% in 6% it had not and in the remaining 6% no information about BP measurements was available.

In the group without BP recordings 96% were men and 4% women in accordance with the fact that women as a routine have their BP measured during pregnancy.

Through an analysis of contacts with the existing Danish health system within the last year the following was found.

Among the non-hospitalized 90% of the population, 531 persons (50%) had consulted in 96 (90%).

Among the non-hospitalized 90% of the population, 531 persons (50%) had consulted their general practitioner where the BP was recorded in 265 cases (50%).

Finally among the non-hospitalized pop-

ulation who had not visited the general practitioner 45 persons (4%) had consulted a specialist, where the BP had been measured in 9 cases (20%).

Thus, approximately two-thirds of the 40 year old population have been in contact with the existing health system within the last year but only in half of the cases had a BP measurement actually been performed.

## References

1. Hagerup, L.M.: Coronary heart disease risk factors in men and women. *Acta med. scand., Suppl.* 357 1974
2. Schroll, M. *Hjertekundersøgelsen af 60-årige mænd og kvinder* Ugeskr. Læg. 138: 113 1976. (English summary).
3. Erikson, M. & Pross Hansen, P. *70-års undersøgelsen i Glostrup* Ugeskr. Læg. 138: 71 1976. (English summary).
4. Rose, G.A. & Blackburn, H. *Cardiovascular survey methods*. WHO 1968
5. Rose, G.A., Hoffman, W.W. & Crowley E.A.: A sphygmomanometer for epidemiologists. *Lancet* i:296, 1964

# Cost of Care of the Hypertensive in the Primary Preventive Trial, Gothenburg

LARS WILHELMSEN GÖRAN BERGLUND and HANS WEDEL  
From the Section for Preventive Cardiology Department of Medicine I  
Sahlgrenska Hospital, Gothenburg, Sweden

To enable a future discussion of priorities with regard to various medical measures it is necessary to take monetary costs and benefits as well as medical benefits into account.

The costs of detecting and treating hypertensives evidently depend upon the structure of the medical care of the community. In larger communities with several doctors and hospitals the system will be more complex and expensive than in a smaller area with only one or a few responsible persons. Screening of the whole community may be necessary to achieve complete control of all hypertensives.

The present report concerns screening and treatment of a random population sample of middle-aged men and is part of a comprehensive primary preventive trial against primarily coronary heart disease (5, 7).

Findings during recent years indicate that close to 95% of middle-aged hypertensives have primary or essential hypertension (8). Very few hypertensives have a secondary form which can be cured by surgical measures. Thus, the demand for extensive examinations of all hypertensives has been reduced considerably.

The costs for drug treatment of hypertensives can vary due to choice of drug; beta-blocking drugs are far more expensive than diuretics. If these two drugs were comparable from a medical point of view the cheaper drug would be recommended. However, the recent findings of a possible cardioprotective role of beta-blockers (2, 9) may have great advantage to hypertensives as most of them are threatened by cardiovascular complications (1).

## Cost of screening

The intervention group of the Primary Preventive Trial comprised one-third of all men in Gothenburg born in 1915-1922 and 1924-1925 or 10 000 men, and 7 455 of these participated.

The total cost of screening, basic care, check-ups and computer processing of data during the years 1970-1973 was 1.4 million Swedish kroner (Skr) recalculated in terms of the value in 1976. The costs for only hypertension screening and processing of these data have been estimated to be 350 000 S.Kr. This gives a cost per person of about 50 S.Kr. or 550 S.Kr. per detected hypertensive (635 detected at the first examination).

## Cost of diagnosis and follow-up

All the men who had screening blood pressures (BP)  $\geq 175$  systolic or  $\geq 115$  diastolic were re-examined within 2 weeks and refer

Table 1. Cost of diagnosis and follow-up of one hypertensive during 5 years. The Primary Preventive Trial, Gothenburg.  
Prices in S.Kr. 1976.

1. Check of diagnosis	
3 BP's by nurse	225
2. Initial lab tests	120
3. Start of control of treatment,	
first year 3 visits to a physician	570
3 visits to a nurse	225
4. Yearly lab tests 4 x 50	200
5. Check ups	
4 visits to a physician	750
12 visits to a nurse	900
Total during 5 years	~ 3 000

Table II. Cost of drugs. The Primary Preventive Trial, Gothenburg.  $N=633$  Prices in S.Kr. 1976.

	%	Per pat./yr	Tot./year
Single drugs			
Beta-blockers	18	600	68 400
Diuretics	14	150	13,350
Combinations			
Beta-bl. + Diuret.	26	750	123 750
Beta-bl. + Hydralaz.	24	800	121 600
Beta-bl. + Diuret. + Hydralaz.	14	950	84,550
Other drugs or comb.	4	750	18 750
Total per year			430 400
Mean per patient during 5 years			~ 3 400

red is a special hypertension clinic for further work-up and treatment. Men with low or BP's were also checked and treated if considered necessary. Two hundred and three men were already on treatment at screening, but had BP's below 175 systolic and 115 diastolic.

The costs during 5 years are shown in Table I. It should be stressed that the real costs, and not only the part of it paid by the patients, are included.

#### Cost of drugs

The various drugs used and the real drug cost appears in Table II.

#### Cost-benefit analysis

Table III summarizes the costs for detection and treatment during 5 years, about 7,000 S.Kr. per hypertensive patient.

Table III. Cost of detection and treatment during 5 years for one hypertensive. The Primary Preventive Trial, Gothenburg. Prices in S.Kr. 1976.

Costs	
Screening	550 (8%)
Diagnosis and follow-up	3,000 (43%)
Drugs	3 400 (49%)
Total per pat.	6,950
Total for 633 pats.	~ 4 400,000

According to recently published results an expected mortality of 8% and incidence of 8% of non-fatal myocardial infarctions were both reduced to about half (1). This indicates that 25 men might have been "saved" by this treatment during the five years. This fairly optimistic view on the effect of treatment has not yet been corroborated by other similar results. Thus, we have to be careful about the interpretation of the results. It should be kept in mind that 82% of the patients were treated by beta-blockers which might have had a specific cardioprotective effect in this study. The total cost per "saved life" can be estimated at 168,000 S.Kr.

#### Comparisons with other studies

The present costs per "saved person" have been compared in Table IV with those of the

Table IV. Cost per hypertensive prevented from death according to severity of hypertension. S.Kr. 1976.

The VA Study	
DBP 115-129	33,500
DBP 90-114	108,000
The Multifactor	
Prev Trial, Gothenburg	163,000

Calculation based on the mean cost of treatment of hypertensives in Gothenburg.

Veterans Administration Studies in the USA (3-4). It is seen that the cost-benefit ratio is better for groups with more advanced hypertension as in the Veterans Administration Studies. It should be pointed out that the screening cut off points 175/115 which were used in the present study are comparable to resting BP's of 162/101 (6). If the prevalence of hypertensive organ manifestations are compared it is also found that most hypertensives in the present study had a less severe hypertension than those in the American Studies. The prevalence of left ventricular hypertrophy according to ECG was four times higher in the Veterans Administration Study with DBP 90-114 mmHg than in the present study.

It is evident that the cost-benefit ratio is dependent upon the severity of hypertension but the costs for saved lives are nevertheless moderate even in moderately severe hypertension.

## References

1. Berglund, G., Wilhelmsen, L., Sannerstedt, R., Hansson L., Andersson O., Sivertsson, R., Wedel H. & Wikstrand, J. Decrease of CHD morbidity by treatment of hypertension. *Lancet* 1978; i: 1.
2. Green, K. Multicentre International Study: Improvement in prognosis of myocardial infarction by long-term  $\beta$ -adrenoreceptor blockade using practolol. *Br. med. J.* 3: 735, 1975.
3. Veterans Administration Cooperative Study Group on Antihypertensive Agents: Effects of treatment on morbidity in hypertension. Results in patients with diastolic blood pressure averaging 115 through 129 mmHg. *J. Amer. med. Ass.* 202:116, 1967.
4. Veterans Administration Cooperative Study Group on Antihypertensive Agents: Effects of treatment on morbidity in hypertension: II. Results in patients with diastolic blood pressure averaging 90 through 114 mmHg. *J. Amer. med. Ass.* 213:1143, 1970.
5. Wilhelmsen, L., Tibblin, G. & Werkö, L. A primary preventive study in Gothenburg, Sweden. *Preventive Medicine* 1: 153, 1972.
6. Wilhelmsen, L., Berglund, G. & Werkö, L. Prevalence and management of hypertension in a general population sample of Swedish men. *Preventive Medicine* 2: 57, 1973.
7. Wilhelmsen, L. Treatment of hypertension in a Swedish Community: the problem of borderline hypertension. *Acta med. scand. Suppl.* 576:99, 1975.
8. Wilhelmsen, L. & Berglund, G. Prevalence of primary and secondary hypertension. *Am. Heart J.* 94:543, 1977.
9. Wilhelmsen, C., Vedin, A., Wilhelmsen, L. & Tibblin, G. Reduction of sudden deaths after myocardial infarction by treatment with alprenolol. *Lancet* ii: 1157, 1974.

# Expenses Concerning Evaluation and Treatment of Hypertension

BIRGITTE JONSSON and TAGE HILDEN

From the Department of Medicine C, Diakoniserstiftelsen, Copenhagen, Denmark

In view of the high frequency of hypertension in the community the costs concerning evaluation and treatment of these patients are of great socio-economic interest. The extent of the examinations, the purpose of which is to identify hypertensive organ damages and to discover any secondary curable forms, is controversial. One of the reasons is the costs involved.

An examination programme regarding patients with high blood pressure referred to an out-patient clinic has been set up (Table I). The physical examination and the circumstances about the blood pressure measurement will not be mentioned in this study. Routine laboratory tests including ECG and X-ray of the chest are recommended for all patients. For patients re-

Table I Recommended examinations in different patient groups.

Examinations	Groups I-IV	No of pts.	
Hemoglobin, serum creatinine, serum potassium urine analysis protein/glucose and microscopy ECG X-ray of the chest	<i>Group I</i> 1. pts. without indication for treatment 2. pts. > 70 years in spite of indication for treatment	52 28	80 34
As above + isotope angiography	<i>Group II</i> pts. with indication for treatment 1. diastolic BP $\geq$ 105 mmHg 2. hypertensive organ damages	76 30	106 46
As above + rapid sequence pyelography	<i>Group III</i> 1. pts. < 50 years, diastolic BP > 115 2. all ages, diastolic BP > 130 3. sudden aggravation of the hypertension 4. drug treatment proves unsatisfactory	27 7 2 7	43 19
As above + renal angiography + renal con- centration in renal veins	<i>Group IV</i> suggestion of renal/renovascular cause of the hypertension		3 1



Veterans Administration Studies in the USA (3-4). It is seen that the cost-benefit ratio is better for groups with more advanced hypertension as in the Veterans Administration Studies. It should be pointed out that the screening cut-off points 175/115 which were used in the present study are comparable to resting BP's of 162/101 (6). If the prevalence of hypertensive organ manifestations are compared it is also found that most hypertensives in the present study had a less severe hypertension than those in the American Studies. The prevalence of left ventricular hypertrophy according to ECG was four times higher in the Veterans Administration Study with DBP 90-114 mmHg than in the present study.

It is evident that the cost-benefit ratio is dependent upon the severity of hypertension, but the costs for saved lives are nevertheless moderate even in moderately severe hypertension.

#### References

1. Berghlund, G., Wilhelmsen, L., Samnerstedt, R., Hansson, L., Andersson, O., Siveriusson, R., Wedel, H. & Wikstrand, J. Decrease of CHD morbidity by treatment of hypertension. *Lancet* 1978, i 1.
2. Green, K. Multicentre International Study: Improvement in prognosis of myocardial infarction by long-term  $\beta$ -adrenoreceptor blockade using practolol. *Br. med. J.* 3 735 1975.
3. Veterans Administration Cooperative Study Group on Antihypertensive Agents. Effects of treatment on morbidity in hypertension. Results in patients with diastolic blood pressure averaging 115 through 129 mmHg. *J. Amer. med. Ass.* 202:116, 1967.
4. Veterans Administration Cooperative Study Group on Antihypertensive Agents. Effects of treatment on morbidity in hypertension. II. Results in patients with diastolic blood pressure averaging 90 through 114 mmHg. *J. Amer. med. Ass.* 213 1143 1970.
5. Wilhelmsen, L., Tibblin, G. & Werkö, L. A primary preventive study in Gothenburg, Sweden. *Preventive Medicine* 1 153 1972.
6. Wilhelmsen, L., Berghlund, G. & Werkö, L. Prevalence and management of hypertension in a general population sample of Swedish men. *Preventive Medicine* 2:57 1973.
7. Wilhelmsen, L. Treatment of hypertension in a Swedish Community: the problem of borderline hypertension. *Acta med. scand., Suppl.* 576:99 1975.
8. Wilhelmsen, L. & Berghlund, G. Prevalence of primary and secondary hypertension. *Am. Heart J.* 94:543 1977.
9. Wilhelmsen, C., Vedin, A., Wilhelmsen, L. & Tibblin, G. Reduction of sudden deaths after myocardial infarction by treatment with alprenolol. *Lancet* ii 1157 1974.

# Expenses Concerning Evaluation and Treatment of Hypertension

BRIGITTE KRINGSHOLM and TAGE HILDEN

From the Department of Medicine C, Diakonissestiftelsen, Copenhagen, Denmark

In view of the high frequency of hypertension in the community the costs concerning evaluation and treatment of these patients are of great socio-economic interest. The extent of the examinations, the purpose of which is to identify hypertensive organ damages and to discover any secondary curable forms, is controversial. One of the reasons is the costs involved.

An examination programme regarding patients with high blood pressure referred to an out-patient clinic has been set up (Table I). The physical examination and the circumstances about the blood pressure measurement will not be mentioned in this study. Routine laboratory tests including ECG and X-ray of the chest are recommended for all patients. For patients re-

Table I. Recommended examinations in different patient groups.

Examinations	Groups I-IV	No. of pts.	n°
Hemoglobin, serum creatinine serum potassium urine analysis protein/glucose and microscopy ECG X-ray of the chest	<i>Group I</i> 1. pts. without indication for treatment 2. pts. > 70 years, in spite of indication for treatment	52 28	80 34
As above + isotope renography	<i>Group II</i> pts. with indication for treatment 1. diastolic BP > 105 mmHg 2. hypertensive organ damages	76 30	106 46
As above + rapid sequence pyelography	<i>Group III</i> 1. pts. < 50 years, diastolic BP > 115 2. all ages, diastolic BP > 130 3. sudden aggravation of the hypertension 4. drug treatment proves unsatisfactory	27 7 2 7	43 19
As above + renal scintigraphy + renin con- centration in renal veins	<i>Group IV</i> suggestion of renal/renovascular cause of the hypertension		3 1

Table II. Distribution of indications for treatment

	Group I	Group II	Group III	Group IV	Total	%
Level of blood pressure only	16	76	29	2	123	88
Cardiac abnormalities	11	21	8	1	41	23
CNS abnormalities	1	5	3		9	5
Cardiac + CNS abnormalities		3	2		5	3
Optic fundi changes (grade III)			1		1	
Pats < 40 years (grade II)		1			1	
Organ damages only	2	4			6	3

quiring treatment isotope renography is suggested. This examination may not be strictly necessary. Rapid sequence pyelography is recommended for the selected patients shown in group III. The choice of isotope renography previous to rapid sequence pyelography is based on the fact that this examination is quicker and more comfortable for the patient and in addition it is less expensive. Finally more complex diagnostic procedures to discover renal/renovascular diseases can be reserved for patients in whom the above mentioned examinations suggest one of these as a cause of hypertension.

In order to demonstrate the distribution of patients into the four groups patients of two particular years 1974 and 1976 were examined retrospectively. The patients were referred to our out-patient clinic by general practitioners because of hypertension, often for reasons of convenience or difficulties in the treatment. The material comprised 232 patients: 110 men and 122 women. The average age was 54 years, 34% under 50 years, 28% from 50 to 59 years and 38% over 60 years old. Table I shows the distribution of the material into the four groups. Less than 2% belonged to group IV.

The indication for treatment II seen in Table II. The level of blood pressure was the only indication in 70% of the cases. Visceral changes were found in 30% and

visceral changes as the only indication in 3%. In 70% of the cases ophthalmoscopic examination was performed by a specialist. Owing to the rare occurrence of premalignant retinal changes ophthalmoscopic examination is not included in the evaluation programmes. It should be mentioned, however, that the examination perhaps ought to be done in young persons having borderline blood pressure.

Table III presents the final therapeutic regimen. A change in the use of drugs has been made, namely from methyl dopa to beta-blockers.

The average expense of medicine per patient was D Kr 4.20 a day a little more in 1976 than in 1974. The cost of examinations in group I is D Kr 350.00, in group II D Kr 500.00, in group III D Kr 700.00 and in group IV D Kr 10 000.00. The calculations are based on the fact that the examinations in groups I, II and III are performed at an out-patient clinic, whereas the examinations in group IV are based on admission to hospital, estimated at 10 days at a price of D Kr 1000.00 each.

The purpose of the present paper is to demonstrate that the vast majority of hypertensive patients can be evaluated at moderate costs. In 80% of the patients referred examinations in group I or II will be adequate, in 18% or 19% group III examinations will be adequate and only in less than 2% will admission to hospital be nec-

Table III. Use of drugs in different diagnostic groups in 1974 and 1976.

	1974 (total 80 pts.)		1976 (total 96 pts.)	
	Groups I + II	Group III	Groups I + II	Group III
Diuretic only	29%	4%	30%	3%
Diuretic + methyldopa	16%	3%	8%	1%
Beta-blocker only	9%	6%	11%	2%
Beta-blocker + diuretic	15%	4%	16%	11%
Beta-blocker + diuretic + vasodilator	1%	8%	3%	7%
Other combinations	5%	1%	8%	

essay Our evaluation programme is of course characterized by the fact that it is carried out at an out-patient clinic. The general practitioner might be still more economical, especially regarding patients not requiring treatment.

It is, however, questionable whether the present material represents the population seen by the general practitioner. To some extent reference to an out-patient clinic may have sorted out very mild cases, and therefore our calculations do not make too favourable an impression of the economic strains.

We think that our experiences may be helpful when the expenses regarding an investigation of the population are to be evaluated in respect to screening, evaluation and treatment of high blood pressure.

#### Discussion:

##### Case:

This, then, is an investigatory programme geared to patients who are referred to a special hypertension clinic. There is no question of it being a limited investigation. Presumably this is an important primary condition.

I would think that the extra examination in groups III and IV are completely un-

necessary if renography in group II is carried out lege artis and shows completely negative results. If the serum creatinine and urine examinations are also normal it would be very very rare to find anything by more extensive examinations. If one wants to go further I do not believe that it should be done with wash-out urography. Then it would be more important to examine the renal vessels direct by angiography.

I do not understand why ophthalmoscopy is not included in the programme. The retina is the only place in the organism where the vessels can be seen direct. Surely it must be very important for a complete evaluation of the patient to know whether there are changes in the retina, especially with regard to the risk of stroke.

##### Hilden:

Giese is probably right in what he says: If the isotope renography is normal, we can at least leave out urography in our group III. After all, it can be combined in various ways. But what we saw as our first concern was to show how large a proportion of patients there are who actually only need a very modest programme of examinations.

Eye examinations are traditionally included in all examinations for hypertension, and at one time have had an enormous importance. Neither would I say that ophthalmoscopy should not be used at least in younger patients, but one should not expect too much from it. If an indication for treatment is based on repeated confirmations of raised diastolic blood pressure, virtually all patients with eye changes will receive treatment and it will not be the eye changes as such that will supply the indication for treatment.

# Standardized Investigation Programme on Patients with Hypertension a Cost Analysis

SVEN ÅKE FÖRQBERG

From the Department of Medicine,  
Borås Hospital, Sweden

Working since 1969 with a standardized programme for hypertension at the medical clinic of Borås Hospital, we have made an attempt to evaluate the costs of what is called a basic or minimized investigation of uncomplicated cases of hypertension.

We imagined an average patient a textile worker as Borås is the textile centre of Sweden. He lives four kilometers from the hospital, works, and when absent his salary is correspondingly reduced. The patient has been referred to the hospital by a doctor during 1973. The hypertension dispensary is part of the activities at the polyclinic of the medical clinic.

On these conditions, we made a flow analysis of all details included in a basic investigation for hypertensives. Table I gives the different steps. The process of patient reference consists of the work of doctors, secretaries and the post office department. The first three visits to the hospital include the diagnostic part. At the third visit the doctor medically examines the patient, completes the special medical

record for hypertensives and starts the treatment. The result of treatment is checked by the dispensary assistant at the fourth visit. At the fifth visit to the doctor the pressure is assumed to be normalized and thereafter follows the regular half year check-ups.

Table II gives an example of how the cost factors at the third visit were analyzed. The time spent at the different working times was estimated from interviews and direct measurements. The working times and the corresponding costs were distributed among the different categories of employees. The salary costs include the employer's social salary expenses to the State.

At Borås Hospital a statement of account is applied which is based on different local organisations, of which the medical polyclinic is one. The polyclinic costs excluding salaries were calculated from the total expenses at the medical polyclinic minus salaries. The patients at the hypertension dispensary were assumed to take a part of these costs proportional to their number in relation to all patients at the medical polyclinic during 1973.

The expenses originating from laboratory analyses were calculated from the scores generally used by Swedish hospital laboratories for their cost analyses.

The patient's loss of net salary was estimated at 45 per cent of the gross income assuming a taxation of 55 per cent. These 55 per cent constitute the State's loss, when the patient does not work, plus 30 per cent of the gross income which is the social salary expense the employer has to pay to the State. Drug expenses were excluded from the study.

Table III comprises the final cost analy-

Table I Basic or minimized investigation in hypertension

- 1 The process of patient reference
- 2 The first visit test sampling by the dispensary assistant
- 3 The second visit pressure measurement by the dispensary assistant
- 4 The third visit medical examination by the doctor Start of treatment.
- 5 Organization of treatment check-ups
- 6 The fourth visit pressure control by dispensary assistant
- 7 The fifth visit the doctor checks the treatment

Table II The first visit to the dispensary assistant

1 The journey of the patient to and from the hospital	
2 Time of absence from work	
3 Test sampling	
a Height	d Blood sample
b Weight	e ECG record
c Urine sample	f Blood pressure measurement
4 Laboratory analyses	
a Urine protein test	f Serum potassium
b Urine glucose test	g Serum urate
c Urine bacterial test	h Serum calcium
d Blood hemoglobin	i Serum cholesterol
e Serum-creatinine	j Serum triglycerides
5 The administration of the patient	
ii Administration of the medical record	

sia Of cost factors "Polliclinic" means the total costs at the medical polliclinic minus salaries to the employees there. The expenses are distributed over the three main carriers of costs. In Sweden "Landstinget" an organization somewhat similar to the county council is responsible for all public medical care.

One should be fully aware of the theoretical character of the presumptions which can be criticised. For example the employer's loss when the worker is excluded from production has not been estimated because we found it impossible. The polliclinic fee the patient has to pay is an income for "Landstinget" and therefore reduces their costs from 265 to 241 kronor. Owing to inflation the sums given in table

III should be increased approximately 30 per cent to get figures valid for 1977.

A detailed flow analysis of investigation-al procedures gives ideas about cost saving changes. The study also discloses the big saving it should mean to organize hypertension dispensary in the evenings for working people and to let nurses employed at industries measure blood pressure under standardized conditions during working hours.

#### Reference

- 1 Forsberg, S.Å. and Oscarsson, C. The content of the basic investigation - a flow analysis and calculation of costs (in Swedish). From Omhändertagande av hypertoni/74 Lindgren & Söner AB, Mölndal, 1975

Table III The final result of the cost analysis given in Swedish kronor

Cost factors	Cost carrier Landstinget	Cost carrier The patient	Loss of taxation The state
Salaries of employees	142		
Polliclinic + postage	48		
Laboratory analyses	75		
Polliclinic fee	24	24	
Travel costs		15	
Loss of salary		141	268
Totals	241	180	268

The sum of subtotals = 689 Swedish kronor

## Discussion:

### Winkler

It is important to separate real economy and financial policy. Forsberg's table contained three columns each of which was interesting, namely the costs of diagnosis and treatment, economic loss to the patient, and the tax loss to society respectively. However, they cannot just be added together. There are two groups of costs that are financially important to society: namely the costs spent on diagnosis and treatment, and the loss of production owing to the patient's examination and treatment. On the other hand, the way in which the patient earns his money does not play an economic role in society even though it is important to the patient himself. Taxes have no real economic importance; they are only transfers of money from one group of society to another.



Table II The first visit to the dispensary assistant.

- 1 The journey of the patient to and from the hospital
- 2 Time of absence from work
- 3 Test sampling
  - a. Height
  - b. Weight
  - c. Urine sample
  - d. Blood sample
  - e. ECG record
  - f. Blood pressure measurement
- 4 Laboratory analyses
  - a. Urine protein test
  - b. Urine glucose test
  - c. Urine bacterial test
  - d. Blood hemoglobin
  - e. Serum-creatinine
  - f. Serum potassium
  - g. Serum urate
  - h. Serum calcium
  - i. Serum cholesterol
  - j. Serum triglycerides
- 5 The administration of the patient
- 6 Administration of the medical record

sis. Of cost factors "Poliklinik" means the total costs at the medical polyclinic minus salaries to the employees there. The expenses are distributed over the three main carriers of costs. In Sweden "Landstinget" an organization somewhat similar to the county council, is responsible for all public medical care.

One should be fully aware of the theoretical character of the presumptions, which can be criticised. For example the employer's loss when the worker is excluded from production has not been estimated because we found it impossible. The polyclinic fee the patient has to pay is an income for "Landstinget" and therefore reduces their costs from 265 to 241 kronor. Owing to inflation the sums given in table

III should be increased approximately 30 per cent to get figures valid for 1977.

A detailed flow analysis of investigation-al procedures gives ideas about cost saving changes. The study also discloses the big saving it should mean to organize hypertension dispensary in the evenings for working people and to let nurses employed at industries measure blood pressure under standardized conditions during working hours.

#### Reference

- 1 Forsberg, S.Å. and Oscarsson, C. The content of the basic investigation - a flow analysis and calculation of costs (in Swedish). From "Omhandertagande av hypertoni/74". Lindgren & Söner AB, Molndal, 1975.

Table III. The final result of the cost analysis given in Swedish kronor

Cost factors	Cost carrier Landstinget	Cost carrier The patient	Loss of taxation The state
Salaries of employees	142		
Poliklinik + postage	48		
Laboratory analyses	75		
Polyclinic fee	24	24	
Travel costs		15	
Loss of salary		141	268
<b>Totals</b>	<b>241</b>	<b>180</b>	<b>268</b>

The sum of subtotals = 689 Swedish kronor

should be allowed to participate in taking the decision of setting up and carrying out the project in the different departments.

The registration can be made using different patients from the accident and emergency department, the out-patient department, the operating theatre department, and the standard acute ward, and the results still can be coordinated so as to give a comprehensive picture of the process involved with treating a typical patient's illness within the hospital.

The results of the preliminary study on the examination, treatment and nursing process within the hospital has now been published, in a report which can be obtained from the

Danish Hospital Institute  
Lindemærket 10  
DK 1119 Copenhagen K  
Denmark.

#### Discussion:

##### Glenn:

The kind of analysis that the Danish Hospital Institute is carrying out where a real effort is made to find out what is being done, is far too rare in the medical world. I think it would be very interesting to know how many superfluous clinical examinations are being made. There are medical departments that completely perform three objective investigations with varying degrees of superficiality and this is rather expensive. Much would be gained by determining how the hypertensive patient should be clinically examined, and at which level of training and experience. There is much talk about how large a role hypertension plays in health costs. I think it is also very important to look at the question from the point of view: How large a percentage of hospitalized patients have problems that in actual fact are caused or complicated by or associated with hypertension? I am thinking in particular of apoplexy and cardiac infarction.

##### Hilden.

There is probably no answer to that question. To the Danish Hospital Institute I would say that in my opinion very few patients with hypertension should be hospitalized, and those are the ones who should be examined by the more complicated methods which require the patient to be kept under close observation. I suppose that that would be 2% - 3%.

##### Henning Poulsen.

The Danish Hospital Institute does not decide who should be hospitalized or who should be treated as out-patients. We only analyse the situation as it is. We believe that hypertension is a suitable disease for inclusion in our investigation programme on examination, treatment and care because here we have the opportunity of evaluating alternative therapy. In the next few years, we shall extend these investigations to cover very large surgical and medical diagnostic groups, so we should get a complete picture of what actually happens with patients in the Danish hospital and health services.

##### Hilden.

I know very well that in Denmark many patients with hypertension are admitted to the medical wards. In reality there are only three kinds of medical patients, the acute, the out-patient and the nursing home patient.

##### Hervald.

No one today can say whether it is better to hospitalize patients or to put them through a programme of out-patient examinations. I think it may be important to get an impression of the 24 hour blood pressure, to see how the initial treatment affects the patient, and to teach the patient to follow the treatment.

# Arterial Hypertension, Examination, Treatment and Nursing Processes in Primary Health Sector and Hospital

NIELS HOLM-NIELSEN MOGENS KJÆRGÅRD HANSEN and HENNING POULSEN  
From the Danish Hospital Institute,  
Copenhagen, Denmark

The Danish Hospital Institute is an independent institution which was set up in 1975 with the main purpose of collecting and disseminating information in the hospital and health service field at the same time carrying out developmental research into planning rationalisation and management. The aim is to provide a better basis for solving the problems faced by the planning and governing authorities within the health services.

The institute has carried out two preliminary studies on the examination, treatment and nursing processes: one within the primary health sector (private practice) and the other correspondingly within the hospital.

The main aim is to develop a system for defining the processes undertaken and to show the extent of the cooperation involved between the two main sectors of health care and the ways in which there is cooperation with the social sector so that the total process of the illness can be established. There is a need for setting out the actual activities which are undertaken during a patient's illness and to that end the processes which result from a diagnosis of arterial hypertension and intertrochanteric fracture of the femur are being registered and analysed.

The pilot study which deals with the activities undertaken by the private practitioner was started in the summer of 1976 and 86 practitioners are taking part representing 53 practices situated in 4 different counties. The choice of the participants covers a variety of conditions, e.g. with regard to distance to the nearest hospital, dispensary and social services, the

number of doctors in the practice, the number of nursing staff available, the number of patients registered with the practice, the way the practice is run and the system used for working shifts etc. The preliminary study will be completed by February 1978. The method which has been developed should with regard to both projects be able to be used locally so that the staff involved will themselves be able to register the information required. This will later form the basis for a general discussion and evaluation to be undertaken at a conference. Here it should be possible for experts to assess the priorities and planning of the services required for the examination, treatment and nursing of the chosen illnesses in Denmark.

The different systems which are in use locally for the examination, treatment and nursing process should be registered and the requirements set out for resources where not only the effect of the treatment is evaluated.

In the same way as with the private practice a similar study has been undertaken during the period of one year to set up a system of evaluation for the hospital sector. The registration has taken place at three university hospital departments: both surgical and medical, standard acute wards and out-patient departments involving over 125 hospital staff of various categories.

The primary study undertaken within the hospital has shown that it is in fact possible to register activities in this way. The differing characteristics of the various departments have shown that it is most important that all the staff groups involved

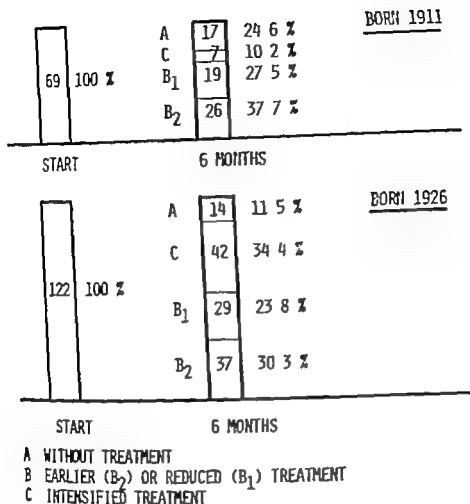


Fig. 1. Antihypertensive treatment of patients born in 1911 and 1926.

drawal of drugs does not cause a rise in the blood pressure, some remaining at the nor-motensive level.

Studies in search of the causes which lead to inappropriate treatment in hypertension are still in progress.

#### References

- 1 Veterans Administration Cooperative Study Group: Return of Elevated Blood Pressure after Withdrawal of Antihypertensive Drugs. *Circulation*, Vol. 51 1107-1113 1975
- 2 Dostan, H.P., Page, I.H., Tarazi, R.C., Frohlich, E.D. Arterial Pressure Responses to Discontinuing Antihypertensive Drugs. *Circulation*, Vol. 37 370-379 1968.
- 3 Page, I.H., Dostan, H.P. Persistence of Normal Blood Pressure after Discontinuing Treatment in Hypertensive Patients. *Circulation*, Vol. 25 433-436, 1962.

# How to Avoid Inappropriate Antihypertensive Treatment

A. EISALO and K.J. TÖTTERMAN

From the First Department of Medicine, University Central Hospital, Helsinki, Finland

*Traditionally early diagnosis of hypertension is stressed followed by adequate treatment and careful follow-up of the patient. The reference point related to these aspects is the normotensive value. On the other hand inappropriate treatment, involving the use of an excessive amount of drugs may result if the hypertensive condition is evaluated only by the normotensive value. A reduction in the administration of use less drugs may lead to a diminution of side effects as well as placing the subject treatment on a sounder economic basis. The purpose of our study is to examine if antihypertensive treatment can be excessive. In this paper we shall show the preliminary results of our progressive study.*

*Helsinki resident hypertensive patients born in the years 1911 and 1926 who have used antihypertensive agents for at least 5 years were selected as the subjects of our study. Their names were obtained from the social insurance files in which all hypertensive patients are listed as they receive the necessary drugs free of charge. Primarily patients who had suffered a stroke, congestive heart failure and renal failure were excluded. A total of 415 were called and 209 were admitted to the study. In the first visit 9 patients were excluded because of hemiplegia, congestive heart failure, intermittent claudication and psychosis. During the first month of the follow-up period 9 dropped out because of an uncooperative attitude, acute psychosis, stroke, and hemiplegia. Thus a total of 191 patients were admitted to follow-up (Fig. 1). Sixty-nine were born in 1911 (30 men and 39 women), 122 were born in 1926 (52 men and 70 women). A complete physical examination including chest X-ray, ECG*

*and serum potassium was taken during the first visit. To date the time span of the follow-up period has reached 9 months.*

*Blood pressure in women born in 1911 (39 patients). In 21 patients the treatment was withdrawn but 13 had to be retreated. In 14 patients a reduction in the daily dosage did not cause a rise in blood pressure, some remaining normotensive. In 3 patients the initial blood pressure reading was high and the treatment had to be intensified.*

*Blood pressure in men born in 1911 (30 patients). In 17 patients the treatment was withdrawn initially. Nine cases had to be retreated. It was possible to reduce the dosage in 5 patients but it had to be intensified in 4 patients.*

*Blood pressure in women born in 1926 (70 patients). In 12 patients the treatment was withdrawn initially. Eight cases had to be retreated. The dosage was reduced in 25 patients initially and the reduction was slowly continued so that it was possible to withdraw the treatment in 7 additional patients. Thus 11 out of the 70 patients were normotensive and did not require any antihypertensive regimen. In 23 patients the treatment had to be intensified.*

*Blood pressure in men born in 1926 (52 patients). Initially in 10 patients the drugs were withdrawn. Seven cases had to be retreated. In 11 patients it was possible to reduce the daily dosage and in 19 it had to be intensified.*

*The preliminary results show that inadequate therapy in hypertension is a problem in all respects. Not only may the normotensive level be unattainable but there is a surprisingly large group in which a reduction of the daily dosage or even with*

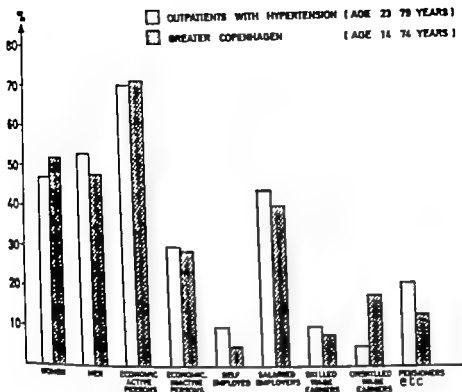


Fig. 1 Employment situation of 277 out-patients with moderate and severe hypertension compared to that of the population in Greater Copenhagen.

economically active women and significantly ( $P < 0.01$ ) more women who receive disability pensions in the group which have been treated for more than 6 years. This difference cannot be due to the small, but insignificant, difference in age groups, neither can it be due to differences in the severity of hypertension (as judged by the

WHO-staging). Though there are more patients with WHO II and III in the group treated for more than 6 years, this difference is far more pronounced among the men.

Two hundred and twenty-eight patients (83% of the material) have or have had an income. Out of these 228 patients, 13%

Table II. Relation between duration of treatment, sex and economic situation among 180 hypertensive patients aged 40 to 60.

	Duration of treatment			
	< 6 years		≥ 6 years	
	Women	Men	Women	Men
Number of patients	48	56	36	40
Mean age (years)	48.7	51.9	51.6	51.7
WHO II + III	29 (60%)	29 (52%)	24 (67%)	36 (90%)
Economically active <sup>a</sup>	46 (96%)	54 (96%)	23 (69%)	33 (96%)
Disability pension	2 (4%)	2 (4%)	11 (31%)	2 (4%)

<sup>a</sup>including housewives and unemployed.

# The Social and Psychological Consequences of being Long term Treated for Moderate and Severe Hypertension

MARTIN DØSSING LIS KELSTRUP and TAGE HILDEN

From the Department of Medicine C, Diakonhøststiftelsen, Copenhagen Denmark

The prognostic advantage of medical treatment of hypertension is well established. The social and psychological consequences of having a blood pressure which requires life-long treatment and frequent controls are less well illuminated. The purpose of this investigation is to draw attention to these aspects of hypertension.

The material includes patients treated at the hypertension out-patient clinic of Diakonhøststiftelsen either because of difficulties of control or for research reasons. The patients have been under observation for so long that the medical treatment has achieved a constant level. We have left out 3 patients in whom other diseases were of more importance with regard to their social situation.

A questionnaire was sent to 305 patients and 277 answered the questions (91%). Issues included in the questions:

- 1 The duration of the antihypertensive treatment. With few exceptions this corresponds to the time the patients have been treated in our out-patient clinic.
- 2 Employment situation and economic situation.
- 3 The influence of hypertension on the employment situation and income.
- 4 The payment of the antihypertensive drugs and the possible strain on the personal economic situation.
- 5 The influence of hypertension on the social and private lives of the patients.

Among the respondents 53% were men and 47% women. Two-thirds of the patients were between 40 and 60 years old, the average age being 53 years.

The results of the WHO-staging and the duration of treatment are shown in Table I.

Table I Severity of hypertension according to WHO criteria. Duration of antihypertensive therapy

Severity of hypertension	Duration of treatment		
WHO I	33%	2 years	13%
WHO II	62%	2-6 years	42%
WHO III	5%	6 years	44%

Most of the patients have visceral changes corresponding to WHO II and have been treated for more than two years.

The employment situation of the patients compared to that of Greater Copenhagen, is shown in Fig. 1. With certain reservations (the proportion of age groups is different and the employment classification of the population of Greater Copenhagen dates from 2 years before ours) the patients will be seen to be about as economically active as the rest of the population. The column "pensioners etc." which includes the disabled pensioners, early old-age pensioners, old-age pensioners, housewives, unemployed and students constitute a relatively higher percentage of the patients. This may be due to the fact that 13% of the patients receive disability pensions and early-old-age pensions because of their hypertension.

In Table II the 40 to 60-year-olds are grouped according to sex and duration of treatment. In each of the four groups it has been shown how many of the patients are economically active (including housewives and unemployed) and how many receive disability pensions owing to hypertension. The economic situation of the men is independent of the duration of treatment, but there are significantly ( $P < 0.01$ ) fewer

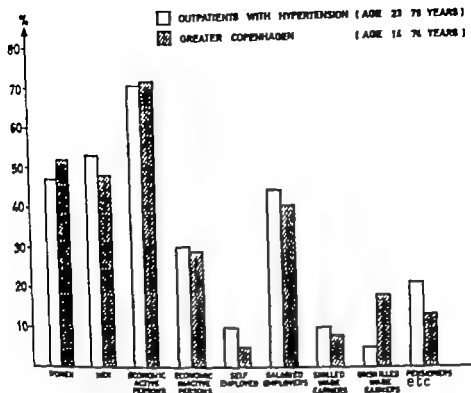


Fig. 1 Employment situation of 277 out-patients with moderate and severe hypertension compared to that of the population in Greater Copenhagen.

economically active women and significantly ( $P < 0.01$ ) more women who receive disability pensions in the group which have been treated for more than 6 years. This difference cannot be due to the small, but insignificant, difference in age groups, neither can it be due to differences in the severity of hypertension (as judged by the

WHO-staging). Though there are more patients with WHO II and III in the group treated for more than 6 years, this difference is far more pronounced among the men.

Two hundred and twenty-eight patients (83% of the material) have or have had an income. Out of these 228 patients, 13%

Table II. Relation between duration of treatment, sex and economic situation among 180 hypertensive patients aged 40 to 60.

	Duration of treatment			
	< 6 years		≥ 6 years	
	Women	Men	Women	Men
Number of patients	48	56	36	40
Mean age (years)	48.7	51.9	51.6	51.7
WHO II + III	29 (60%)	29 (52%)	24 (67%)	36 (90%)
Economically active*	46 (96%)	54 (96%)	25 (69%)	38 (96%)
Disability pension	2 (4%)	2 (4%)	11 (31%)	2 (4%)

\* Includes those who are themselves and unemployed.



Table III Influence of hypertension on the patients activities

The influence of hypertension on the patients life in general (n = 265)

No influence	39%
Little influence	36%
Strong influence	15%
Do not know	10%

The influence of hypertension on the patients private life (n = 257)

No influence	54%
Little influence	25%
Strong influence	8%
Do not know	13%

have suffered a decrease in wages without changing their jobs and 6% have had to change their jobs with a decrease of wages as a consequence.

In Denmark the National Health Insurance pay three-quarters of the expenses of antihypertensive drugs for all patients. Patients with low income also have the last one-quarter paid by social support but two-thirds of our patients pay the last one-quarter themselves. Of these patients 28% feel this as a certain strain on the economy.

Table III shows the distribution of answers to questions as to whether hypertension affects the social and private lives of the patients. About 50% feel that the hypertension is a strain on their daily life as it means decreased working capacity no travelling no more sport etc.

Approximately one-third of the patients think that their hypertension has a negative influence on their private lives in the form of less time with the family poorer marital relations and less surplus energy to take care of the children. Among the male patients stating that the influence on their private life is strong many gave impotency as the cause. Most of these patients were given beta-blocking treatment and by looking through the journals in retrospect, it turned out that few of these patients had mentioned their impotency to the doctor at the out-patient clinic.

The results of the investigation only refer to patients with moderate and severe hypertension who can be treated as out patients. Mild cases of hypertension are referred to their general practitioners and very severe cases with disabling complications cannot be treated as out-patients.

The investigation shows that the patients are almost as economically active as the rest of the population of Greater Copenhagen. Those among the patients who can not keep their jobs are women who before giving up their jobs had a low occupational position and had their house work to do and had been treated for more than 6 years.

One has to be cautious when concluding from a vertical investigation based on questionnaires. On the other hand, a considerable part of the patients feel that a number of limitations in their way of life are consequences of their disease and the medical treatment and this must be taken seriously.

# Programmed Medical Care in Hypertension

## Concepts and Ideas

SVEN AXE FORSBERG

From the Department of Medicine,  
Stock Hospital, Sweden

According to published results conventional medical care of hypertension tends to be of bad quality (4-5). By conventional means medical care asked for by the patients at polyclinics or practitioners, where many different diseases are treated by doctors in a way depending on the experience and knowledge of the individual doctor.

The consequence must be for society to aim at the creation of an alternative and better medical care for hypertensives. This alternative is programmed medical care. This implies that skilled people develop a plan and strategy for detection, investigation, treatment and control of a disease or disorders. The details of a programme must be locally modified due to varying local conditions.

In Sweden the first attempt to develop a programme for hypertension started in 1969 (2). In 1975 the National Board of Health and Welfare in Sweden appointed a committee with the purpose of developing programmes for diabetes, hypertension, urinary tract infection, lump in the breast, hernia and acute tablet intoxication. The programme for hypertension is in progress.

A group of strictly scientifically oriented people is doomed to fail in developing a programme applying to primary medical care far away from universities. A project committee must contain representatives from different levels of medical care and different levels of medical employees.

Until nationwide blood pressure screening programme is organised in Sweden, if ever we shall learn to detect hypertension more often than hitherto by letting blood

pressure recording become much more of a routine method in medical care. This can be best accomplished by leaving blood pressure measurement in the hands of nurses and medical aids, by definition of minimal action-demanding pressure level and by creating local channels whereby patients with hypertension can be easily transferred for further investigation.

A basic investigation in hypertension is focused around "The five questions"

- 1 Hypertension?
- 2 Affection of the heart, the kidneys, or the brain?
- 3 What stage of hypertension?
- 4 Curable hypertension?
- 5 Does the clinical picture influence choice of therapy?

The first question deals with quality of blood pressure measurements, repeated measurements and definition of minimal action-demanding pressure level.

The second question is about indication for therapy and long term prognosis.

With answers to the first two questions there is also an answer to the third in terms of WHO' classification system for example.

Excluding hypertension caused by oral contraceptives, curable hypertension seems to constitute not more than a few per thousand of all unselected hypertensives (1). Certain simple tests, such as palpation of the femoral pulsations, tests for urinary protein and bacteria, analyses of serum creatinine and potassium, can call attention to patients with secondary hypertension of which only a few may be curable. In other

Table III Influence of hypertension on the patients activities

The influence of hypertension on the patients life in general (n = 265)

No influence	39%
Little influence	36%
Strong influence	15%
Do not know	10%

The influence of hypertension on the patients private life (n = 257)

No influence	54%
Little influence	25%
Strong influence	8%
Do not know	13%

have suffered a decrease in wages without changing their jobs and 6% have had to change their jobs with a decrease of wages as a consequence.

In Denmark the National Health Insurance pay three-quarters of the expenses of antihypertensive drugs for all patients. Patients with low income also have the last one-quarter paid by social support but two-thirds of our patients pay the last one quarter themselves. Of these patients 28% feel this as a certain strain on the economy.

Table III shows the distribution of answers to questions as to whether hypertension affects the social and private lives of the patients. About 50% feel that the hypertension is a strain on their daily life as it means decreased working capacity no travelling no more sport etc.

Approximately one-third of the patients think that their hypertension has a negative influence on their private lives in the form of less time with the family poorer marital relations and less surplus energy to take care of the children. Among the male patients stating that the influence on their private life is strong many gave impotency as the cause. Most of these patients were given beta-blocking treatment and by looking through the journals in retrospect, it turned out that few of these patients had mentioned their impotency to the doctor at the out-patient clinic.

The results of the investigation only refer to patients with moderate and severe hypertension who can be treated as out-patients. Mild cases of hypertension are referred to their general practitioners, and very severe cases with disabling complications cannot be treated as out-patients.

The investigation shows that the patients are almost as economically active as the rest of the population of Greater Copenhagen. Those among the patients who cannot keep their jobs are women, who before giving up their jobs, had a low occupational position and had their housework to do and had been treated for more than 11 years.

One has to be cautious when concluding from a vertical investigation based on questionnaires. On the other hand a considerable part of the patients feel that a number of limitations in their way of life are consequences of their disease and the medical treatment and this must be taken seriously.

# Programmed Medical Care in Hypertension

## Concepts and Ideas

SVEN ÅKE FOLSTENBERG

From the Department of Medicine  
Borås Hospital, Sweden

According to published results conventional medical care of hypertension tends to be of bad quality (4-5). By conventional means medical care is asked for by the patients at polyclinics or practitioners, where many different diseases are treated by doctors in a way depending on the experience and knowledge of the individual doctor.

The consequence must be for society to aim at the creation of an alternative and better medical care for hypertensives. This alternative is programmed medical care. This implies that skilled people develop a plan and strategy for detection, investigation, treatment and control of a disease worth treating. The details of a programme must be locally modified due to varying local conditions.

In Sweden the first attempt to develop a programme for hypertension started in 1969 (2). In 1975 the National Board of Health and Welfare in Sweden appointed a committee with the purpose of developing programmes for diabetes, hypertension, urinary tract infection, lump in the breast, hernia and acute tablet intoxication. The programme for hypertension is in progress.

A group of strictly scientifically oriented people is doomed to fail in developing a programme applying to primary medical care far away from universities. A project committee must contain representatives from different levels of medical care and different levels of medical employees.

Until a nationwide blood pressure screening programme is organised in Sweden, if ever we shall learn to detect hypertension more often than hitherto by letting blood

pressure recording become much more of a routine method in medical care. This can be best accomplished by leaving blood pressure measurement in the hands of nurses and medical aids, by definition of minimal action-demanding pressure level and by creating local channels whereby patients with hypertension can be easily transferred for further investigation.

A basic investigation in hypertension is focused around "The five questions

- 1 Hypertension?
- 2 Affection of the heart, the kidneys, or the brain?
- 3 What stage of hypertension?
- 4 Curable hypertension?
- 5 Does the clinical picture influence choice of therapy?

The first question deals with quality of blood pressure measurements, repeated measurements and definition of minimal action-demanding pressure level.

The second question is about indication for therapy and long term prognosis.

With answers to the first two questions there is also an answer to the third in terms of WHO's classification system for example.

Excluding hypertension caused by oral contraceptives, curable hypertension seems to constitute not more than a few per thousand of all unselected hypertensives (1). Certain simple tests, such as palpation of the femoral pulsations, tests for urinary protein and bacteriuria, analyses of serum creatinine and potassium, can call attention to patients with secondary hypertension of which only a few may be curable. In other

Table III Influence of hypertension on the patients' activities.

The influence of hypertension on the patients' life in general (n = 263)

No influence	39%
Little influence	36%
Strong influence	15%
Do not know	10%

The influence of hypertension on the patients' private life (n = 257)

No influence	54%
Little influence	25%
Strong influence	8%
Do not know	13%

have suffered a decrease in wages without changing their jobs and 6% have had to change their jobs with a decrease of wages as a consequence.

In Denmark the National Health Insurance pay three-quarters of the expenses of antihypertensive drugs for all patients. Patients with low income also have the last one-quarter paid by social support, but two-thirds of our patients pay the last one-quarter themselves. Of these patients 28% feel this as a certain strain on the economy.

Table III shows the distribution of answers to questions as to whether hypertension affects the social and private lives of the patients. About 50% feel that the hypertension is a strain on their daily life as it means decreased working capacity, no travelling, no more sport etc.

Approximately one-third of the patients think that their hypertension has a negative influence on their private lives in the form of less time with the family, poorer marital relations and less surplus energy to take care of the children. Among the male patients stating that the influence on their private life is strong, many gave impotency as the cause. Most of these patients were given beta-blocking treatment and by looking through the journals in retrospect, it turned out that few of these patients had mentioned their impotency to the doctor at the out-patient clinic.

The results of the investigation only refer to patients with moderate and severe hypertension who can be treated as out-patients. Mild cases of hypertension are referred to their general practitioners and very severe cases with disabling complications cannot be treated as out-patients.

The investigation shows that the patients are almost as economically active as the rest of the population of Greater Copenhagen. Those among the patients who cannot keep their jobs are women, who before giving up their jobs had a low occupational position and had their housework to do and had been treated for more than 6 years.

One has to be cautious when concluding from a vertical investigation based on questionnaires. On the other hand a considerable part of the patients feel that a number of limitations in their way of life are consequences of their disease and the medical treatment and this must be taken seriously.

## References

1. Berglund, G., Andersson, O. and Wilhelmsen, L.: Prevalence of primary and secondary hypertension: studies in a random population sample. *Brit. med. J.* 2:554 1976.
2. Faurberg, S.Å.: Dispensaries for treatment of hypertension (in Swedish). Paper read at Medicinsk Ekstremum, Stockholm 1970.
3. Faurberg, S.Å.: Maximal investigation of hypertension in different forms of primary medical care (in Swedish). *Nordisk Symposium. Hypertension*. Göteborg 1973 p. 221. Eds. Vedin, A., Wilhelmsen, C., and Werkö, L., Lindgren & Söner AB, Göteborg 1973.
4. Tibblin, G.: High blood pressure in men aged 30 - a population study of men born in 1913. *Acta med. scand., Suppl.* 470 1967.
5. Wilhelmsen, L., Berglund, G., and Werkö, L.: Prevalence and management of hypertension in a general population sample of Swedish men. *Prev. Med.* 2:57 1973.

cases only special and individual clinical traits should motivate extended investigations

Question five mainly deals with diabetes, gout and obstructive lung disease.

By basic or minimized investigation we mean the degree of evaluation that every patient should be guaranteed (3). It should be adequate for the great majority of patients. The basic investigation at Borås Hospital lacks roentgen picture of the lungs and heart, i.v. pyelography and renography. We do not check urinary concentration capacity and do not make a urine culture. This policy was first met with opposition but recent epidemiological studies have given support to the idea of a simple but consistent investigational programme in uncomplicated cases. It is even economically necessary if we are to be able to treat all hypertensives who can be helped.

A programme for hypertension can be applied within the frames of conventional medical care for example by a general practitioner. One can also concentrate hypertensives at particular times of the week and thereby perhaps rationalize the work. An alternative is to organize special dispensaries for hypertensives with personnel trained to do their job. All three forms of organization are probably appropriate under particular conditions.

Two concepts should be used: one the minimal action-demanding blood pressure, the other the minimal treatment-demanding blood pressure. By minimal action-demanding pressure I mean the lowest pressure level recorded on a single occasion motivating further action such as repeated measurements under standardized conditions possibly together with a basic investigation. Minimal treatment-demanding pressure should be defined on the basis of the mean of at least three pressure measurements under standardized conditions. At a certain level the pressure alone indicates therapy and at a specified lower level treatment may be considered together with contributing indications such as heredity, sex, secondary organ injury or other cardiovascular risk factors.

A hypertension programme should include at least three drugs for use in the majority of patients. It is reasonable to have a thiazide drug and a beta-blocker. What the third drug should be one cannot be dogmatic about. At Borås we use hydralazine. The choice of alternative drugs in case of side effects or therapeutic failure is yet more uncertain. I myself mostly give furosemide, spironolactone or methyldopa.

It is important to distinguish the phase of blood pressure lowering from the phase of control of a pressure which has been normalized. One is a dynamic, the other a static phase. After a long time of normal pressure one can often, but not always, decrease the amount of medication. This ought to be systematically tested according to the principle of minimized medication to achieve normotension.


The control of hypertension must be of a defensive implying that all patients should get written information about time of control and patients who fail to appear for control should be actively traced. Several studies show that such a policy secures good adherence to therapy. Information to the patient about hypertension also helps the patient to stick to therapy. Therefore all patients should get a booklet about hypertension. In Sweden there are presently about six different booklets to choose between.

Home pressure recording is another element of information to the patient about his disease. In some cases it is a good help during phases of changing therapy. However, more research about home pressure recording is needed to exploit the full potential of its use.

Some final words of warning. We, who start the big and heavy wheels of a machine, must also look at means to brake these wheels so that they do not run away. We must remember that even if we practically must work with the concept of minimal treatment-demanding pressure, we do not really know what that is, either medically or economically. Presently we simply make the best possible guess.

## MANAGEMENT PROGRAM FOR HYPERTENSION

THE COUNTY OF  
SKARABORG  
260 000 inhabitants  
16 municipalities

 The area for management program for  
hypertension  
Total population 140 000

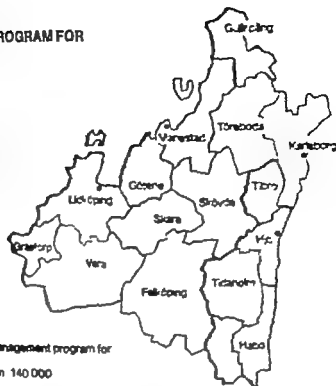


Fig. 1. A map of the county of Skaraborg indicating the trial and control areas

control area. The programme is started step-wise. In the first step the management of already known hypertensive patients will be improved through the introduction of special guidelines for diagnosis, treatment and follow-up. These guidelines will be detailed below. In the second step hitherto unknown hypertensives will be traced through the introduction of an obligatory blood pressure measurement for all patients seeking attendance at the primary services, i.e. general physicians and health physicians. This applies only to patients 40-69 years of age. Under that age hypertension is infrequent and firm criteria for treatment cannot be set, and in older patients treatment is less obligatory. Special routines have been worked out for the handling of subjects with hypertension. Newly detected cases as well as previously known hypertensives will be taken care of at The Health Care Centres at which an afternoon per week has been devoted to care of hypertensive patients. An outpa-

tient hypertension clinic has been started at the Central Hospital in Skövde which is the largest town in Skaraborg County and the centre for the Skaraborg project. The central hypertension clinic should serve as a referral station for hypertensive patients refractory to ordinary treatment and for patients with suspected secondary hypertension.

During the third step a complete control of the hypertensive disease is sought to be attained in the whole study area. Subjects with borderline blood pressure will be followed by repeated blood pressure measurements. Diagnostic work-up and treatment will be given in accordance with the guidelines below.

### Guidelines for diagnosis, treatment and follow-up

The subjects (40-69 years of age) who are found to have blood pressure above 170 systolic and/or 105 diastolic at the first measurement are offered a check-up within



# The Skaraborg Project - A Controlled Trial Regarding the Effect of Structured Hypertension Care

GÖRAN BERGLUND SVEN-OLOF ISACSSON and LARS RYDÉN

From the Department of Medicine I University of Gothenburg  
Department of Preventive Medicine and Department of Medicine  
the Central Hospital Skövde, Sweden

During autumn 1976 and spring 1977 a care programme for hypertension was worked out. This programme is now carried out with start July 1 1977. The work with the programme was initiated by SPRI the Swedish Planning and Rationalization Institute of the Health and Social Services who also financed its development.

The background to the growing interest in methods for a better management of hypertension is the fact that high blood pressure is a disease which occurs with a high frequency and is associated with a high risk for future cardiovascular diseases. Diseases related to hypertension impose the greatest burden on somatic hospital care in Scandinavia. Half of the hypertensives are unknown to the medical care system and only every seventh hypertensive patient has an acceptable blood pressure control. The health care system in its present form has not been able to overcome this disease.

**The working out of the care programme**  
This started with a meeting at which all medical staff of the involved area, i.e. physicians and nurses, were gathered for an informal lecture about the situation regarding high blood pressure in the county. At this meeting it was discussed how the situation might be improved a working group was created and its tasks were set up (Table I). The first task was to work out guidelines for the detection diagnosis, treatment and follow up of hypertensive patients in the County of Skaraborg. This work was performed in close contact with

Table I Structure and responsibilities of the central hypertension unit

---

## 1. Structure

- A) Chief cardiologist at the central hospital and chief physician at the department of preventive medicine
- B) One district physician
- C) One physician from the department of medicine
- D) Two nurses.

## 2. Definition of duties

- A) To design the hypertension care programme
  - B) Continual follow up of medical progress and revision of the care programme.
  - C) Training of personnel.
  - D) Coordination of hypertension care in the County
  - E) Collection of data.
  - F) Processing of data
  - G) To guarantee management of referred hypertensive patients with complications
- 

representatives for the different categories of medical personnel involved. The programme was later officially accepted by vote by the Medical Board of Skaraborg County Council.

## The realization of the programme

Owing to lacking financial resources and to make an evaluation possible the county was divided into two halves both with around 140 000 inhabitants (Fig. 1). The care programme is carried out in one part, the study area, but not in the other the



# The Skaraborg Project - A Controlled Trial Regarding the Effect of Structured Hypertension Care

GÖRAN BERGLUND SVEN-OLOF ISACSSON and LARS RYDÉN

From the Department of Medicine I University of Gothenburg  
Department of Preventive Medicine and Department of Medicine  
the Central Hospital, Skövde, Sweden

During autumn 1976 and spring 1977 a care programme for hypertension was worked out. This programme is now carried out with start July 1 1977. The work with the programme was initiated by SPRI the Swedish Planning and Rationalization Institute of the Health and Social Services who also financed its development.

The background to the growing interest in methods for a better management of hypertension is the fact that high blood pressure is a disease which occurs with a high frequency and is associated with a high risk for future cardiovascular diseases. Diseases related to hypertension impose the greatest burden on somatic hospital care in Scandinavia. Half of the hypertensives are unknown to the medical care system and only every seventh hypertensive patient has an acceptable blood pressure control. The health care system in its present form has not been able to overcome this disease.

## The working out of the care programme

This started with a meeting at which all medical staff of the involved area, i.e. physicians and nurses were gathered for an informal lecture about the situation regarding high blood pressure in the county. At this meeting it was discussed how the situation might be improved, a working group was created and its tasks were set up (Table I). The first task was to work out guidelines for the detection, diagnosis, treatment, and follow-up of hypertensive patients in the County of Skaraborg. This work was performed in close contact with

Table I Structure and responsibilities of the central hypertension unit.

---

### 1. Structure

- A) Chief cardiologist at the central hospital and chief physician at the department of preventive medicine.
- B) One district physician.
- C) One physician from the department of medicine.
- D) Two nurses.

### 2. Definition of duties

- A) To design the hypertension care programme.
  - B) Continual follow-up of medical progress and revision of the care programme.
  - C) Training of personnel.
  - D) Coordination of hypertension care in the County.
  - E) Collection of data.
  - F) Processing of data.
  - G) To guarantee management of referred hypertensive patients with complications.
- 

representatives for the different categories of medical personnel involved. The programme was later officially accepted by vote by the Medical Board of Skaraborg County Council.

## The realization of the programme

Owing to lacking financial resources and to make an evaluation possible the county was divided into two halves both with around 140 000 inhabitants (Fig. 1). The care programme is carried out in one part, the study area, but not in the other, the

Treatment is started with either a diuretic or with a beta-receptor blocking agent. The first drug of choice has been left to the physician in charge of the patient, as no valid proof of the superiority of one of the two drugs over the other could be found. If normotension is not obtained with the first drug the alternative drug of the two mentioned above, is instituted. If a normal blood pressure cannot be obtained with this combination, hydralazine will be added. Patients resistant to this triple drug combination will be referred to the central hypertension clinic for evaluation and treatment.

After the institution of therapy the patients are followed-up at intervals that are determined by the severity of the disease and by the response to the given treatment. Yearly controls including history taking, physical examination and some simple laboratory tests are done. Both at these yearly follow-ups and at the initial investigations, special record forms precoded for direct punching and computerization were used. A copy of the record forms is sent to the organizing centre.

### Evaluation

An initial baseline survey performed before the programme was started, showed that the study area and the control area were comparable with regard to frequency and severity of hypertension, prevalence of cardiovascular diseases, and socio-economic variables. The evaluation will try to answer the following questions:

Will the programme be:

1. Feasible in the way it is outlined?
2. Effective in preventing or postponing hypertensive complications?
3. Defensible from humanitarian point of view (i.e. to what extent will reduced suffering from reduced morbidity and mortality outweigh any harmful effects of the programme)?
4. Defensible from an economic point of view (i.e. to what extent will any economic gains from reduced morbidity and mortality make up for the costs of the programme)?

The last two points of the evaluation programme will not be discussed here as the outline for these analyses are not yet finished.

The first point of evaluation, i.e. whether it is feasible to carry out the programme the way it is outlined should be answered already during the first two years of the programme. If the majority of the physicians in the study area can be persuaded to follow the programme that is if they detect, diagnose, treat and follow-up hypertensive patients according to the programme, then it can be said that it was feasible to carry out the programme. The problem will be to find out whether the physicians in the study area really follow the intended protocol.

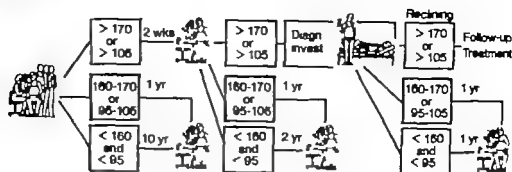
Whether patients with hypertension will be examined, treated and followed up in accordance with the programme, will be followed by checking the copy of the file which is sent to the central unit. These records contain data on the diagnostic work-up, blood pressure during follow-up, frequency of side effects, and frequency of and reason for drop-out. These data are necessary for judging whether the programme can be carried out as intended.

The medical effectiveness will be evaluated by combining two methods. All death certificates for both the study and the control areas will be collected continually. The cause of death will be coded by a person who is unaware of the group to which the certificate belongs. Total death rates and specific causes can then be compared between the two areas. Non-fatal strokes and myocardial infarctions will be followed in both areas by means of a simple stroke and infarction register. The medical effectiveness will then be calculated as the difference in incidence of these terminal points between the study and control areas.

Care programmes of the kind described here are in progress for several other diseases such as diabetes mellitus and breast cancer. A care programme will, for obvious reasons, impose great changes in our present work. It is therefore important for these programmes to be properly evalu-

# CRITERIA FOR CONTINUED FOLLOW UP AND DIAGNOSTIC INVESTIGATION

Age 40-60 years



Under 40 years and over 60 years

	Too high	Borderline	Normal
> 60 year	> 180 or > 110	170-180 or 105-110	< 170 and < 105
< 40 year	> 180 or > 95	155-180 or 90-95	< 155 and < 90

Fig 2 Blood pressure limits for different age groups and suggested times for continued follow-up.

**2 weeks** Those who still have pressure above these limits are examined according to a standardized diagnostic work up. If they still are "hypertensive" they are put on antihypertensive treatment and followed-up. The proposed management for other blood pressure categories is shown in Fig 2. The limits for normal pressure shown in Fig 2 also indicate the values to which increased blood pressure should be reduced.

The diagnostic work up includes blood pressure measurement, history taking and a physical examination, ECG and some simple laboratory tests (Table II). In certain cases, but not as a rule, X-ray of the heart, intravenous pyelography or isotope renography might be performed.

Hypertensive subjects with hypertensive organ involvement such as left ventricular hypertrophy, cardiac enlargement, albuminuria or increased S-creatinine will be

Table II Basic investigation.

Medical history
Physical examination
ECG
Laboratory test (S-electrolytes, S-creatinine, S-cholesterol, S-urate; urinary test for albuminuria and glucosuria)

treated as well as subjects with three blood pressure measurements above the criteria for hypertension. Persons with borderline blood pressure elevations might be given treatment if the physician finds that other factors such as serum lipids and family history might worsen the prognosis of the patient.

Information to the patient is given both by the physicians and the nurses. A special pamphlet with advice to patients with high blood pressure has been worked out.

# Drug of First Choice in Mild and Moderate Essential Hypertension Clinical Hemodynamic and Economic Aspects

PER LUND-JOHANSEN

From the Medical Department A,  
University of Bergen, Norway

At what stage in the hypertensive process drug therapy should be started and which drug should be given the first choice is still uncertain. Conventional clinical trials with a treatment group and a control group are very difficult to use, because the well known clinical complications develop so late in mild and moderate essential hypertension. The largest trials until now the Veterans Administration Cooperative Study Group on antihypertensive agents (12) and the US Public Health Service Hospitals Study (10), were mainly based on thiazide diuretics plus reserpine. Although both studies demonstrated no significant benefit from therapy on myocardial infarction, both studies reported less left ventricular hypertrophy in the treated group compared to the controls.

Animal experiments have demonstrated that in several types of hypertension, a gradual restructuring of the high pressure compartments appears very early when the blood pressure is raised (1). Drug intervention in the pre-hypertensive phase has prevented these changes (2).

In man with essential hypertension the earliest changes in the heart and in the resistance vessels are less well known and biopsy studies are lacking for obvious reasons. Functional studies on the central hemodynamics at rest and during exercise may however tell more than conventional clinical studies. In a follow-up study of the central hemodynamics in 33 subjects below the age of 40 years left untreated over a period of 10 years, it was shown that although no complications could be demonstrated by conventional clinical methods (clinical examination, ECG, ophthalmoscopy, urine examination) the stroke vol-

ume had decreased and the total peripheral resistance had increased more than was expected from aging alone. (8-9).

In 8 of these subjects the blood pressure had increased (the mean arterial pressure at rest sitting from 116 mmHg to 125 mmHg), and further observation was found unethical. Drug treatment with a non-cardioselective beta-blocker benidrolol, was started. The blood pressure decreased in all subjects. After one year on the beta-blocker the hemodynamic study was repeated. The mean arterial pressure at rest sitting decreased from 125 mmHg to 108 mmHg (13%) but there was no normalization in the central hemodynamics. The total peripheral resistance rose further (10%) and the cardiac index decreased (22%) (Fig. 1).

Studies during exercise demonstrated a marked decrease in the heart rate and in the cardiac index, no compensatory increase in the stroke volume and an increase in the calculated total peripheral resistance, changes resembling those seen by the use of other non-cardioselective beta-blockers (6). Thus, although the beta-blocker had decreased the blood pressure, central hemodynamics were not changed in a normal direction.

Another study demonstrated that during prolonged beta-blocker therapy over 3 years, there was no further normalization of the central hemodynamics, but on the other hand, no further increase in the total peripheral resistance or decrease in the cardiac index. Studies on a cardioselective beta-blocker atenolol, showed slightly more favourable changes (7).

ated before they are promoted to definite diagnostic and therapeutic moulds for a whole country. We have found it necessary to evaluate the feasibility as well as the medical effectiveness and humanitarian and economic defensibility. For other diseases where there is full agreement on how the disease should be treated it will be possible to make the evaluation easier by excluding evaluation of the medical effectiveness. Unfortunately it is still valid for many major diseases that opinions are divided regarding the value of different forms of treatment. When this is the case evaluation of the medical effectiveness remains most important.

#### Reference

- 1 Berglund O, Isacson, S-O & Rydén, L.: Vårdprogram för högt blodtryck. Skaraborgs läns landsting. Spri-rapport 3 52, Stockholm 1977

#### Discussion.

##### *Puska*

The programme applies primarily to hypertension but it will also apply to other risk factors. It is not only a matter of primary prevention but also of secondary prevention. Is it possible to evaluate the effect of this?

##### *Berglund*

We will probably not be able to separate the effect of hypertension treatment and the effect on the treatment of other risk factors which, without doubt, will be better in the intervention area than in the control area.

##### *Puska*

How will you make sure that the registration of myocardial infarction and apoplexy is comparable in the intervention and control areas?

##### *Berglund*

We will not have the opportunity of letting one doctor make the diagnosis by visiting all hospitals and examining every single patient, but we have agreed on common diagnostic criteria, which are found in writing at every clinic in the area. The validity of the register will be evaluated in smaller groups of patients.

As regards comparison between the intervention and control areas we have already carried out a base-line survey on a sub-sample comprising 8% in both areas in order to verify that they were comparable with regard to cardio-vascular mortality and morbidity and blood pressure. We also intend to conclude with a terminal survey to determine if the changes in these important factors are the same in the two areas in 7 years time when the programme will finally be evaluated.

2. Folkow B. Structural changes in heart and vessels during hypertension with aspects on their reversibility. *N.Z. J. Med.*, Suppl. 2, 6, 25, 1976.
3. Lambert, D.M.: Hypertension and myocardial infarction. *Brit. med. J.* 3:685 1974.
4. Lund-Johansen, P.: Hemodynamic changes in long-term diuretic therapy of essential hypertension. *Acta med. scand.* 187:509 1970
5. Lund-Johansen, P. Hemodynamic changes at rest and during exercise in long-term prazosin therapy of essential hypertension. In: Prazosin: Evaluation of new anti-hypertensive agent (ed. H.W.K. Othman), p. 43. *Excerpta Medica* 1974.
6. Lund-Johansen, P. Hemodynamic long-term effects of furosemide at rest and during exercise in essential hypertension. *Acta med. scand.* 199:261, 1976.
7. Lund-Johansen, P. Hemodynamic long-term effects of new beta-blocker atenolol (ICI 66082) *Brit. J. clin. Pharmacol.* 3:445 1976.
8. Lund-Johansen, P. Hemodynamic alterations in hypertension: spontaneous changes and effects of drug therapy. A review. *Acta med. scand.*, Suppl. 603: 1 1977
9. Lund-Johansen, P. Central hemodynamics in essential hypertension. *Acta med. scand.*, Suppl. 606:35 1977
10. McPhee Smith, W. Edlevick, S.A. & Kresh, W.M., U.S. Public Health Service Hospitals Intervention trial in mild hypertension. In: Hypertension: Diuretics, Complications and Intervention. (ed. G. Oweid & R. Kline), Grune & Stratton Inc., New York and London 1978. In press.
11. Veda, J.A. & Wilhelmsson, C.E. Long-term post-infarction treatment with prazosin. *Brit. med. J.* 4:579 1977
12. Veterans Administration Cooperative Study Group on Antihypertensive agents: Effects of treatment on morbidity in hypertension II. *J. Amer. med. Ass.* 213:1143, 1970

## Discussions:

### Hakén.

I feel that the hemodynamic considerations Lund-Johansen has presented here are perhaps a little too sharp. Others, at least, have found that the primary rise in peripheral resistance decreases with beta-blockers. As for diuretics, you yourself have found a decreased cardiac output in certain situations, so one cannot just say

that diuretics only affect the peripheral resistance. It may be rather by chance that one drug is used first instead of the other because in many cases, perhaps almost all, a combination of a diuretic and a beta-blocker will be used in the end.

### Lund-Johansen.

There is some misunderstanding about the effect of beta-blockers on vascular resistance. Trials with propranolol in patients who had been examined before treatment, after acute administration and then after some months treatment have shown that vascular resistance rises acutely then gradually decreases and ends at about the same level as it was before treatment. Consequently due to the rise in the vascular resistance immediately after treatment is started and when the cardiac output is decreased, there is little effect on the blood pressure. Gradually as time passes, the vascular resistance is decreased but levels lower than the starting point are rarely obtained. The cardiac output remains reduced about 15%.

I believe there is a fundamental difference in the circulation of individuals on long term thiazide treatment and individuals on long term beta-blocker treatment. There is a great difference in the pulse frequency because diuretics do not affect the pulse frequency either resting or during physical exercise, while beta-blockers induce a drastic reduction. All the five beta-blockers I have investigated induce a fall in the cardiac output, and during physical exercise in particular it is considerably lower than normal. I am surprised that individuals tolerate it as well as they seem to do but I would not be surprised if future investigations show that a hypokinetic circulation like this may prove unfortunate. Therefore, the effect of these drugs on the circulation is quite different. But on the other hand by using diuretics we introduce electrolyte changes, changes in the uric acid and carbohydrate metabolism. The plasma volume is also changed and will remain decreased during long term therapy about 7%.



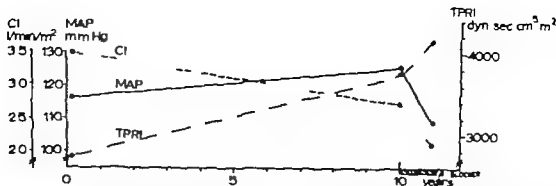


Fig. 1 Cardiac Index (CI) mean arterial pressure (MAP) total peripheral resistance index (TPRI) during 10 years without treatment followed by 1 year on beta-blocker (benitrolol)  $n=8$  Sitting Position rest.

The *thiazide diuretics* induce a different hemodynamic pattern reduction in the total peripheral resistance without changes in the heart rate or stroke volume during exercise (4). In a group of 6 patients between 40 and 49 years old when first studied and treated with a thiazide as a sole drug during ten years the blood pressure decreased from 134 mmHg to 103 mmHg (23%). Although there was some decrease in the cardiac index over ten years there was no further increase in the total peripheral resistance in contrast to a similar group of patients left untreated for ten years. Thus the thiazides seem to induce a decrease in total peripheral resistance during the first year of treatment, and from then on no significant increase over the next decade.

The more recent antihypertensive agent *prazosin* induces a different hemodynamic pattern a marked decrease in the total peripheral resistance, an increase in the stroke volume and cardiac index at rest as well as during exercise. Thus this drug induces a normalization of the central hemodynamics over a period of one year. More prolonged studies are lacking (5).

The *side-effects* of the three types of drugs, the thiazides the beta-blockers and prazosin are well known and usually acceptable, when the conventional contraindications are respected.

There are large differences between these three types of drugs when the economy is taken into consideration. The thiazide diuretics are much cheaper than the beta

blockers and prazosin. The price for one year's treatment with a conventional thiazide preparation will be about 200 Norwegian kroner (N Kr), with a conventional cardioselective beta-blocker N Kr 1,200 and with prazosin about N Kr 700 per patient.

Thus the thiazides may still defend their position as the drug of first choice in mild and moderate hypertension. Prazosin with very promising hemodynamic characteristics has still been used for too short a time to allow a definite conclusion with respect to its position as a possible drug of first choice.

With respect to the beta blockers it should be emphasized that death from myocardial infarction or a malignant arrhythmia is the greatest threat for patients with mild and moderate hypertension. It is possible that beta blockers may protect against these lethal complications (3, 11). If this is going to be documented in further studies, it is likely that the beta blockers will definitely replace the thiazides as the drug of first choice. It is even possible that the anti-arrhythmic effect might be more important than the blood pressure lowering effect in this type of patient.

## References

- 1 Folkow B. Vascular changes in hypertension: review and recent animal studies. In: Pathophysiology and Management of Arterial Hypertension (Eds. O. Bergholm, L. Hansson & L. Werkö), p. 95. Lindgren & Soner AB, Göteborg 1975.

2. Folkow B. Structural changes in heart and vessels during hypertension with aspects on their reversibility. *N.Z. J. Med.*, Suppl. 2, 6, 35, 1976.
3. Lambert, D.M.. Hypertension and myocardial infarction. *Brit. med. J.* 3:685 1974
4. Lund-Johansen, P. Hemodynamic changes in long-term diuretic therapy of essential hypertension. *Acta med. scand.* 187:309 1970.
5. Lund-Johansen, P. Hemodynamic changes at rest and during exercise in long-term prazosin therapy of essential hypertension. In: *Prazosin Evaluation of new anti-hypertensive agent* (ed. D.W.K. Cotton), p. 83 Excerpta Medica 1974
6. Lund-Johansen, P. Hemodynamic long term effects of thiazol at rest and during exercise in essential hypertension. *Acta med. scand.* 199:263, 1976.
7. Lund-Johansen, P.J. Hemodynamic long-term effects of new beta-blocker atenolol (ICI 60082) *Brit. J. clin. Pharmacol.* 3 445 1976.
8. Lund-Johansen, P. Hemodynamic alterations in hypertension spontaneous changes and effects of drug therapy. A review. *Acta med. scand.*, Suppl. 603 1 1977
9. Lund-Johansen, P. Central hemodynamics in essential hypertension. *Acta med. scand.*, Suppl. 606 35 1977
10. McFarr Smith, W. Edervitch, S.A. & Krushat, W.M.. U.S. Public Health Service Hospitals intervention trial in mild hypertension. In: *Hypertension: Determinants, Complications and Interventions*. (ed. G. O'Carroll & R. Kilmer), Grune & Stratton Inc., New York and London 1978. In press.
11. Veda, J.A. & Wilhelmsen, C.E.. Long-term post-infarction treatment with practolol. *Brit. med. J.* 4:579 1975
12. Veterans' Administration Cooperative Study Group on Antihypertensive agents: Effects of treatment on morbidity in hypertension II. *J. Amer. med. Ass.* 213:1143 1970.

## Discussion:

### Notes.

I feel that the hemodynamic considerations Lund-Johansen has presented here are perhaps a little too sharp. Others, at least, have found that the primary rise in peripheral resistance decreases with beta blockers. As for diuretics, you yourself have found a decreased cardiac output in certain situations, so one cannot just say

that diuretics only affect the peripheral resistance. It may be rather by chance that one drug is used first instead of the other because in many cases, perhaps almost all, a combination of a diuretic and a beta-blocker will be used in the end.

### Lund-Johansen.

There is some misunderstanding about the effect of beta blockers on vascular resistance. Trials with propranolol in patients who had been examined before treatment, after acute administration and then after some months treatment have shown that vascular resistance rises acutely then gradually decreases and ends at about the same level as it was before treatment. Consequently due to the rise in the vascular resistance immediately after treatment is started and when the cardiac output is decreased there is little effect on the blood pressure. Gradually as time passes, the vascular resistance is decreased but levels lower than the starting point are rarely obtained. The cardiac output remains reduced about 15%.

I believe there is a fundamental difference in the circulation of individuals on long term thiazide treatment and individuals on long term beta-blocker treatment. There is a great difference in the pulse frequency because diuretics do not affect the pulse frequency either resting or during physical exercise, while beta-blockers induce a drastic reduction. All the five beta-blockers I have investigated induce a fall in the cardiac output, and during physical exercise in particular it is considerably lower than normal. I am surprised that individuals tolerate it as well as they seem to do but I would not be surprised if future investigations show that a hypokinetic circulation like this may prove unfortunate. Therefore, the effect of these drugs on the circulation is quite different. But on the other hand by using diuretics we introduce electrolyte changes, changes in the uric acid and carbohydrate metabolism. The plasma volume is also changed and will remain decreased during long term therapy about 7%.

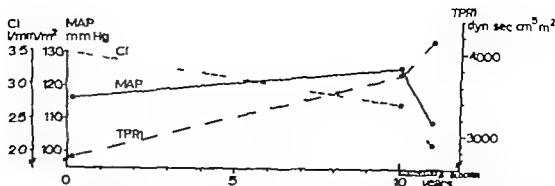


Fig. 1 Cardiac index (CI) mean arterial pressure (MAP), total peripheral resistance index (TPRI) during 10 years without treatment followed by 1 year on beta-blocker (buntitrolol).  $n = 8$  Sitting Position rest.

The thiazide diuretics induce a different hemodynamic pattern reduction in the total peripheral resistance without changes in the heart rate or stroke volume during exercise (4). In a group of 6 patients between 40 and 49 years old when first studied and treated with a thiazide as a sole drug during ten years the blood pressure decreased from 134 mmHg to 103 mmHg (23%). Although there was some decrease in the cardiac index over ten years there was no further increase in the total peripheral resistance in contrast to a similar group of patients left untreated for ten years. Thus the thiazides seem to induce a decrease in total peripheral resistance during the first year of treatment and from then on no significant increase over the next decade.

The more recent antihypertensive agent, prazosin, induces a different hemodynamic pattern a marked decrease in the total peripheral resistance, an increase in the stroke volume and cardiac index at rest as well as during exercise. Thus this drug induces a normalization of the central hemodynamics over a period of one year. More prolonged studies are lacking (5).

The side-effects of the three types of drugs the thiazides the beta-blockers and prazosin are well known and usually acceptable, when the conventional contraindications are respected.

There are large differences between these three types of drugs when the economy is taken into consideration. The thiazide diuretics are much cheaper than the beta

blockers and prazosin. The price for one year's treatment with a conventional thiazide preparation will be about 200 Norwegian kroner (N.Kr.) with a conventional cardioselective beta-blocker N.Kr. 1,200 and with prazosin about N.Kr. 700 per patient.

Thus the thiazides may still defend their position as the drug of first choice in mild and moderate hypertension. Prazosin with very promising hemodynamic characteristics has still been used for too short a time to allow a definite conclusion with respect to its position as a possible drug of first choice.

With respect to the beta-blockers it should be emphasized that death from myocardial infarction or a malignant arrhythmia is the greatest threat for patients with mild and moderate hypertension. It is possible that beta-blockers may protect against these lethal complications (3-11). If this is going to be documented in further studies it is likely that the beta-blockers will definitely replace the thiazides as the drug of first choice. It is even possible that the anti-arrhythmic effect might be more important than the blood pressure lowering effect in this type of patient.

## References

- Folkow B. Vascular changes in hypertension: review and recent animal studies. In: Pathophysiology and Management of Arterial Hypertension (Eds. G. Berglund, L. Hansson & L. Werkö), p. 95. Lindgren & Söder AB Göteborg 1975.

# The Organisation of Treatment of Hypertension the Role of the General Practitioner

SHOUD HUMERFELT

From the Institute of General Practice,  
University of Bergen, Norway

The majority of hypertensive patients in Norway are taken care of by the general practitioner (GP). However we know very little in what way these patients are screened, treated and followed-up in practice. The following problems arise:

- Which diagnostic procedures are used by the GP?
- How many are taken care of by the GP without consulting a specialist or a hospital?
- Which are the criteria for referral?
- How are the follow-up routines?
- How does the GP evaluate the effectiveness of the treatment?

## 1. Standardization of methodology

At our institute we have felt the need for a standardized technique. This applies to several of the postgraduate training programmes. These programmes are built on:

- a. A video-tape on diagnostic procedures and recommendations for therapy
- b. A pamphlet "Hypertension in General Practice" presenting the most important clues of the diagnostic, therapeutic and follow up procedures.
- c. Introduction programmes on the measurement of BP and on the technique of ophthalmoscopy adapted by Professor J.A. Osterhuis, Leyden.

These programmes have been presented at several courses for practitioners.

## 2. The contribution of the GP to hypertension surveys and therapeutic controls

During the last 5-6 years the need for studies on hypertensives under the supervision of the GP has been realized, especially in our country with a system of decentralised health service.

Some examples.

1. The Peripress treatment survey. This drug was primarily accepted for the use of specialists only because of the initial side effects. Further studies were initiated to investigate these first-dose phenomena. Several groups of GPs (totally 142) joined in a cooperative study. Based upon these results of a low initial dosage programme, this drug is now available for general prescription.
2. Several other surveys are in the hands of GPs. The intervention programme, initiated by the State Mass X-ray Department in the County of Finnmark in Sogn and Fjordane. After a screening programme all hypertensives are regularly followed-up and treated by the district doctors and GPs.
3. A cooperative study initiated by the Institute of General Practice in Oslo, the Section of Clinical Pharmacology and Toxicology at Ullevål Hospital, the Directorate of Health, and the Institute of Pharmacotherapy University of Oslo, has recently taken place in two counties in Norway.

The main aim of this investigation was to study more closely the GP's methods of screening and treatment and their follow up routines. In all, 154 GPs have taken part in this comprehensive survey.

## Discussion:

### Holte:

As a general practitioner interested in hypertension, I have the impression that the treatment and check-up of hypertension is poor. What is the reason for this? Is it because the doctor lacks information? or the

I would also question the possible effect of beta blockers direct on the heart. We have still not been able to prove such an effect in the treatment of hypertension, but I would mention that at present a multi-centre study is being carried out here in Scandinavia, conducted from Gothenburg. Several centres are involved, for example Karelia, other groups in Sweden and groups in Iceland. We need many patients to be able to show the difference in mortality between the two drug choices. We have estimated that we need about 4 000 patients and at the moment there are only about 1 000.

# Doctor Patient Relationship in Long term Treatment of Hypertension

H. STORM-MATHISEN and K. HEBNES

From the Deaconess Hospital Lovisenberg,  
Oslo, Norway

There are many different ways of evaluating a doctor-patient relationship and compliance with a therapeutic regimen. One obvious way is to measure the serum level of the prescribed drug or the urine excretion of the metabolites (1). These methods can only be used in a limited number of patients and for a relatively short observation time. The tablet counting is more convenient in the long-term treatment.

Also an interview might lead to better doctor-patient relationship and seems to be a fairly adequate method for evaluating patient compliance (2, 3).

An indicator of the compliance to therapy over the years in treatment of a chronic disorder like hypertension is probably to study the number of drop-outs from follow-up (4, 5).

In the Deaconess Hospital (Lovisenberg sykehus), Oslo we have in collaboration with several general practitioners treated and checked-up thousands of hypertensive patients. In the period 1955-1975 we have registered 145 patients under our own treatment for a minimum of one year and in the mean more than 111 years.

After 1965 this method has been followed.

- 1 The patient is called with a letter to a polyclinic interview and investigation at a given date and time. The waiting time is not more than a few minutes. The laboratory study is done at the same time.
- 2 The patients are examined about twice a year or more if necessary. The examination by the physician lasts for about half an hour. The patient's use of tablets is checked on these occasions and side effects are discussed. Also the other parts

of the regimen, smoking, diet, etc. are discussed. Blood pressure is measured in sitting and standing position, and standing after five knee bendings.

- 3 Reports and results concerning laboratory findings are given in a letter to the patient together with a written message about the new dosage of tablets and the new appointment day and hour. The most convenient time for this has already been discussed during the consultation.

- 4 Blood pressures are plotted on millimetre paper size 21 x 29 cm (A4). The notes for many years are collected in a loose leaf book after a system with cued-Metbydopa, beta-blocker spirooctone etc. according to the leading drug treatment.

- 5 Address-cards with cues are collected in special boxes. The main register has signals for cross reference given to this special hypertension register.

Results of compliance (drop-out) from 1 1.65 1 10 77 (Table I): 192 patients (124 men and 68 women) who began treatment during the period 1965-70 were investigated: 1 this material we had 10 drop-outs with unknown destiny.

Six of these had been treated by other physicians on the hospital staff. We had 4 drop-outs of patients treated by ourselves, 1 after one year, 1 after two years, 1 after three years and 1 after four years of treatment before satisfactory blood pressure values were attained. Side-effects such as values were attained. Side-effects such as impotence and feeling uncomfortable led patients to stop treatment in these cases. In 3 patients treatment could be stopped because the blood pressure remained nor

has failed to make up his mind on hypertension questions? If the latter is the case how can it be remedied? Perhaps practitioners ought to take part in the research and help in the development of research projects

*Humerfeldt*

I quite agree with Holte's point of view. The four institutes in Norway who are working on the primary health service problems have also collaborated on a research committee.

# Doctor Patient Relationship in Long-term Treatment of Hypertension

H. STORM-MATHISEN and K. HEBNES  
From the Deaconess Hospital Lovisenberg,  
Oslo, Norway

There are many different ways of evaluating a doctor-patient relationship and compliance with a therapeutic regimen. One obvious way is to measure the serum level of the prescribed drug or the urine excretion of the metabolites (1). These methods can only be used in a limited number of patients and for a relatively short observation time. The tablet counting is more convenient in the long-term treatment.

Also, an interview might lead to better doctor-patient relationship and seems to be a fairly adequate method for evaluating patient compliance (2, 3).

An indicator of the compliance to therapy over the years in treatment of a chronic disorder like hypertension is probably to study the number of drop-outs from follow-up (4, 5).

In the Deaconess Hospital (Lovisenberg sykehus), Oslo we have in collaboration with several general practitioners treated and checked-up thousands of hypertensive patients. In the period 1955-1975 we have registered 745 patients under our own treatment for a minimum of one year and in the mean more than 10 years.

After 1965 this method has been followed.

1. The patient is called with a letter to a polyclinic interview and investigation at a given date and time. The waiting time is not more than a few minutes. The laboratory study is done at the same time.
2. The patients are examined about twice a year or more if necessary. The examination by the physician lasts for about half an hour. The patient's use of tablets is checked on these occasions and side effects are discussed. Also the other parts

of the regimen, smoking, diet, etc. are discussed. Blood pressure is measured in sitting and standing position, and standing after five knee bendings.

3. Reports and results concerning laboratory findings are given in a letter to the patient together with a written message about the new dosage of tablets and the new appointment day and hour. The most convenient time for this has already been discussed during the consultation.
  4. Blood pressures are plotted on millimetre paper size 21 x 29 cm (A4). The notes for many years are collected in a loose leaf book after a system with codes: Methyldopa, beta-blocker, spironolactone etc. according to the leading drug treatment.
  5. Address-cards with codes are collected in special boxes. The main register has signals for cross reference given to this special hypertension register.
- Results of compliance (drop-out) from 1: 65; 10-77 (Table I): 192 patients (124 men and 68 women) who began treatment during the period 1965-70 were investigated. In this material we had 10 drop-outs with unknown destiny.

Six of these had been treated by other physicians on the hospital staff. We had 4 drop-outs of patients treated by ourselves, 1 after one year, 1 after two years, 1 after three years and 1 after four years of treatment before satisfactory blood pressure values were attained. Side-effects such as impotence and feeling uncomfortable led patients to stop treatment in these cases. In 3 patients treatment could be stopped because the blood pressure remained low.



Table 1 Patient compliance in long-term antihypertensive treatment.

Drop-out study						
1 1 65	1 1 70		192 patients (124 men 68 women)			
per 1 10 77	Non-compliance		Treatment stopped	Changed address and doctor		Total
	Unknown	Treatment stopped Not Improved	Improved	Compliance	non-comp	
Men	4(+4)	4(+0)	1	17	4	34
Women	0(+2)	0(+2)	2	7	0	13
Total	4(+6)	4(+2)	3	24	4	47

The treatment has been started in the period from 1 1 65 to 1 1 70

The patients have been followed up until 1 10 77

Figures in brackets indicate patients treated by associated doctors.

mal for several years without drugs. Twenty-eight patients left the district and changed physicians. Of these patients 24 had regular appointments with the new physician. Only 4 of them dropped out of treatment. The non-compliance rate for the given period 1965-1977 was found to be roughly 10% or roughly 1% per year.

We found it most important to shorten the waiting time in connection with check-up consultations and the taking of blood for investigation. The waiting-room and the office are given a pleasant appearance. The appointments are given by mail but flexible and most convenient for the patient. In Oslo we have a relatively steady population without too much moving which is favourable for this type of study. We feel that the best method for increasing compliance is to combine treatment with teaching and small discussions about hypertension and other problems concerning health and well being. Our policy has always been to inform the patients about the results of blood pressure measurements and laboratory findings. We have found that only in this way are we able to keep our patients as collaborators in our attempts to control their hypertension.

#### References

- 1 Lowenthal, D.T. et al. Patient compliance for antihypertensive medication. The usefulness of urine assays. *Curr Ther Res.* 19:405 1946
- 2 Åberg, H. Patient Compliance. *Acta med. scand. Suppl.* 606:25 1977
- 3 Eljertsson, G. Vad tycker befolkningen om sjukvården? *Nord. Med.* 91:313 1976.
- 4 Caldwell, J.R. et al. The drop out problem in antihypertensive treatment. A pilot study of social and emotional factors influencing a patient's ability to follow antihypertensive treatment. *J chron. Dis.* 22:579 1970
- 5 Flannery, F.A. Jr, Martle, E.C. & Flannery, F.A. Hypertension in the inner city I. Analysis of Clinic drop outs. *Circulation* 47:73 1973





# Acta Medica Scandinavica

Supplementum 627

## Proceedings of SYMPOSIUM ON ECHOCARDIOGRAPHY

Lund, Sweden

May 13–14, 1977

Edited by

Arne Gustafson and Stig Persson

# Acta Medica Scandinavica

originally published as *Nordiskt Medicinskt Arkiv* was founded in 1869 by Professor Axel Key MD. In 1901 (from volume 34) this journal was divided into a medical and a surgical section. Since 1919 (from volume 52) the medical section has been published under the name of *Acta Medica Scandinavica*.

## *Acta Medica Scandinavica*

publishes papers on general medicine mainly from Denmark, Finland, Iceland, Norway, Sweden and the Netherlands. Short preliminary reports (not exceeding two pages) will be published as short notices. The papers are published in English, French or German. *Acta Medica Scandinavica* is published on a non-profit basis.

## *Subscriptions*

to *Acta Medica Scandinavica* (two volumes of six numbers each annually) include free supplements to the current volumes.

## *Subscription Rates*

Per annum = two volumes.

In Denmark, Finland, Iceland, Norway, Sweden and the Netherlands: Sw kr 330 incl. postage. Swedish subscribers add VAT.

Other countries: Sw kr 375 incl. postage.

## *Chief Editor*

Professor Jan G. Waldenström, MD  
*Acta Medica Scandinavica*  
Kungsgatan 54  
S-111 35 Stockholm, Sweden

## *Editorial Office*

*Acta Medica Scandinavica*  
Kungsgatan 54  
S-111 35 Stockholm, Sweden  
(All correspondence concerning manuscripts and editorial matters)  
Telephone 08/21 77 53

## *Subscription Distribution and Advertising*

The Almqvist & Wiksell Periodical Company  
Gamla Brogatan 26, Box 62  
S-101 20 Stockholm 1, Sweden

## *Printers*

Almqvist & Wiksell Tryckeri AB  
S-751 81 Uppsala, Sweden

Proceedings of  
SYMPOSIUM ON  
ECHOCARDIOGRAPHY

Lund, Sweden  
May 13–14 1977

Edited by  
Arne Gustafson and Stig Persson

# Acta Medica Scandinavica

originally published as *Nordiskt Medicinskt Arkiv* was founded in 1869 by Professor Axel Key MD. In 1901 (from volume 34) this journal was divided into a medical and a surgical section. Since 1919 (from volume 52) the medical section has been published under the name of *Acta Medica Scandinavica*.

## *Acta Medica Scandinavica*

publishes papers on general medicine mainly from Denmark, Finland, Iceland, Norway, Sweden and the Netherlands. Short preliminary reports (not exceeding two pages) will be published at short notice. The papers are published in English, French or German. *Acta Medica Scandinavica* is published on a non-profit basis.

## *Subscriptions*

to *Acta Medica Scandinavica* (two volumes of six numbers each annually) include free supplements to the current volumes.

## *Subscription Rates*

Per annum = two volumes.

In Denmark, Finland, Iceland, Norway, Sweden and the Netherlands: Sw. cr. 330 incl. postage. Swedish subscribers add VAT.

Other countries: Sw. cr. 375 incl. postage.

## *Chief Editor*

Professor Jan G. Waldenström, MD  
*Acta Medica Scandinavica*  
Kungsgatan 54  
S-111 35 Stockholm, Sweden

## *Editorial Office*

*Acta Medica Scandinavica*  
Kungsgatan 54  
S-111 35 Stockholm, Sweden  
(All correspondence concerning manuscripts and editorial matters)  
Telephone 08/21 77 63

## *Subscription, Distribution and Advertising*

The Almqvist & Wiksell Periodical Company  
Gamla Brogatan 26 Box 62  
S-101 20 Stockholm 1, Sweden

## *Printers*

Almqvist & Wiksell Tryckeri AB  
S-751 81 Uppsala, Sweden

In 1953 Inge Edler and Hellmuth Hertz started their pioneer work resulting in the paper "The use of ultrasonic reflectoscope for the continuous recording of movements of the heart walls" in the proceedings of Kungliga Fysiografiska Sällskapet in Lund in 1954. At that time these two scientists could hardly anticipate that they had given birth to a method of investigation which would turn out to be of an almost revolutionizing importance for the examination of patients with heart disease.

After an initial period when the method was mainly used for diagnosing mitral valve stenosis and pericardial effusion, echocardiography was become widely used in the morphological and functional evaluation of most heart diseases. Only by use of echocardiography we have possibilities to estimate the real frequency of diseases as idiopathic hypertrophic subaortic stenosis and prolaps of the mitral valve.

The importance of echocardiography is also clear from the fact that its different methods of application have captured a rapidly growing part of cardiological literature during the last decade. During this period an important technical development has taken place, above all the introduction of two-dimensional echocardiography which has enlarged the possibilities of investigating the anatomy and function of the heart.

This symposium was arranged as a mark of honour to Inge Edler at his retirement from the appointment as head of the Cardiological Clinic at the University Hospital of Lund. It was intended to give an understanding of the place of echocardiography to-day and its possibilities of development in the future.





Accuracy and usefulness of echocardiography in acute myocardial infarction H S Mäkinen and J Helkimo	152
Cross sectional echocardiographic evaluation of changes in ventricular shape in the ischaemic and non ischaemic left ventricle A E Weyman	164

#### SYMPOSIUM ON CONGENITAL HEART DISEASE

Echocardiographic assessment of left ventricular function during the postoperative period in children operated on because of congenital heart disease G Björkhem and W R Lundström	178
Pulmonary valve motion in valvular pulmonary stenosis in childhood C Rey and J M Lablanche	185
Echocardiography in the diagnosis of subaortic stenosis W R Lundström	192
Two-dimensional echocardiography in atrioventricular canal malformation. A diagnostic approach H A Y Daanans, H K P J Voogd, C M Ligtoet, J Ridder and A C G Wenink	
Preliminary experiences in 1 and 2 dimensional contrast echocardiography R D Müller, F Olet, J Stenbauer and K Bühlmeier	203
Echocardiographic identification of the aorta and pulmonary artery in transposition of the great arteries A B Houston, M L Gregory, E M Coleman and A Shaw	210

#### FREE COMMUNICATIONS

Single-element echocardiography by multi-element automatic sequential line-selection W R Lundström and R Hansson	212
Echocardiographic findings in cardiac tamponade R J Hagel	217
Echocardiographic findings in ventricular septal rupture anterior wall aneurysm complicating myocardial infarction H Egeblad and S Hansen	224
Quantitative analysis of left ventricular filling phase by echocardiography P Brana, C Oddou, E Beraldo, A Kulas, F Laurent, A Philippon and F De Vernejoul	230

## CONTENTS

### TWO-DIMENSIONAL ECHOCARDIOGRAPHY, TECHNIQUE AND CLINICAL APPLICATION

Principles of two-dimensional real time echocardiography imaging  
P R Goldberg

The cross-sectional echocardiogram in clinical cardiology Applications and relationship to the M-mode technique  
A E Weyman

Improvement of lateral resolution in ultrasonic systems  
H Bom C T Lancee and C M Ligtoet

Ultrasound fluoroscopy - what is it and our approach to your requirements  
J A McLain

Phased array cardiac imaging System operation results and clinical role  
J A Kisslo

The clinical utility of two dimensional echocardiography  
H Rakowski R P Martin J W French and R L Popp

### SYMPOSIUM ON LEFT VENTRICULAR FUNCTION

Technical aspects of single transducer echocardiography  
M S Nieminen

The study of left ventricular function by M-mode echocardiography  
D G Gibson

Influence of pharmacologic intervention and valvular heart disease on left ventricular ejection phase indices A review  
A D Hagan

Left ventricular function Assessment by wide angle two dimensional ultrasonic sector scanning  
H Rakowski R P Martin and R L Popp

Evaluation of the left ventricle by two-dimensional echocardiography  
J A Kisslo

Cross-sectional echocardiographic assessment of aortic obstruction  
A E Weyman

### SYMPOSIUM ON ISCHEMIC HEART DISEASE

The use of M-mode echocardiography in ischemic heart disease  
D G Gibson

Effect of increases in afterload on the systolic thickening of acutely ischemic myocardium An experimental echocardiographic study  
R E Kerber M E Marcus J Ehrhardt and F M Abboud

Accuracy and usefulness of echoventriculography in acute myocardial infarction H S Nieminen and J Helkälä	152
Cross sectional echocardiographic evaluation of changes in ventricular shape in the ischaemic and non ischaemic left ventricle A.E. Heyman	164

#### SYMPOSIUM ON CONGENITAL HEART DISEASE

Echocardiographic assessment of left ventricular function during the postoperative period in children operated on because of congenital heart disease B Björkhem and W R. Lundström	178
Pulmonary valve motion in valvular pulmonary stenosis in childhood E Rey and J M Lablanche	185
Echocardiography in the diagnosis of subaortic stenosis W R Lundström	192
Two-dimensional echocardiography in atrioventricular canal malformation A diagnostic approach H A V Praetorius, H P J Voogd, C M Ligtwet, J Ridder and A.C.G. Merink	
Preliminary experiences in 1 and 2 dimensional contrast echocardiography E D Miller, F Glet, J Stenbæk and K Buhlmeier	203
Echocardiographic identification of the aorta and pulmonary artery in transposition of the great arteries A B Houston, M L Gregory, E M Coleman and A. Shaw	210

#### FREE COMMUNICATIONS

Single-element echocardi-tomography by multi-element automatic sequential line-selection W R. Lundström and R. Hansson	212
Echocardiographic findings in cardiac tamponade R.J. Hagel	217
Echocardiographic findings in ventricular septal rupture anterior wall aneurysm complicating myocardial infarction H Egebløed and S. Hansen	224
Quantitative analysis of left ventricular filling phase by echocardiography P. Bran, B. Oddou, E. Beraldo, A. Kulas, F. Laurent, A. Philippon and F. De Vernejoul	230



# PRINCIPLES OF TWO-DIMENSIONAL REAL TIME ECHOCARDIOGRAPHY IMAGING

P R GOLDBERG

*From the Biomedical Research and Development Brith-Kline Instruments  
Sunnyvale California.*

## INTRODUCTION

Two-dimensional ultrasonic imaging has developed over the past two decades from a research tool into a viable diagnostic modality. Though the use of this technique for cardiac imaging is relatively new, a large number of devices have been developed for the expressed purpose of performing this task. Since ultrasonic images can be derived by many different methods, these instruments are not all based on the same physical principles. For an echocardiographic visualization system to provide the greatest diagnostic utility, it must employ concepts which are dictated by the clinical need. It is the purpose of this discussion to start with basic clinical needs and ultrasonic imaging physical principles and describe, in steps, the development of a two-dimensional real time ultrasonic visualization system ideally suited for cardiac imaging.

## 1.0 BASIC CLINICAL NEEDS

All medical diagnostic instrumentation has been created for the same purpose: that is, to provide the clinician with detailed information directly related to the condition of the internal organs of the body. An echocardiographic imaging system performs this task by utilizing ultrasonic energy to form a two-dimensional image of the structures of the heart. What characteristics should this image possess if it is to be of maximum diagnostic utility? On the surface, this appears to be a simple question with one answer. The image displayed should be a distortion-free representation of the cardiac structures.

Without a doubt, the display of non-distorted cardiac images is the goal of all ultrasonic visualization systems. However, there are significant impediments to the realization of this ideal. From a clinical standpoint, the visualization system must capture the details of a rapidly moving object through an echocardiographic "window" which varies greatly in size from patient to patient. As stated by Dr. Harvey Feigenbaum in the second edition

of his book entitled Echocardiography published by Lea & Febiger sound travels poorly through a gaseous medium such as air. It is not possible for ultrasound to traverse any significant amount of lung tissue and still obtain adequate echoes from the heart. The acoustic mismatches between bone and soft tissue is great. If one tries to direct the sonic beam through bone, almost all of the ultrasonic energy is reflected or absorbed. Thus an echocardiographic examination is impractical if the transducer is placed over the sternum or rib. This problem may not be as great with infants or young children since the ribs and even sternum may not be calcified. However, in adults one is limited as to how the echocardiographic examination is performed with respect to transducer placement. The usual echocardiographic "window" is between the second and fifth intercostal spaces within 3 to 4 cm to the left of the sternal border. One can usually examine the heart from at least two or sometimes three interspaces. In many adult patients the second interspace has lung overlaying the heart and is a difficult location for the echocardiographic examination. In some adults with low diaphragms even the third or fourth interspace might be extremely difficult because of overlaying lung. On the other hand, in children the higher interspaces are commonly available for the echocardiographic examination and in young infants the transducer can probably be placed right over the sternum and the ribs if necessary.

These clinical realities are the starting point for the development of the perfect two dimensional real time echocardiographic imaging system. They indicate that the visualization system of choice will have the following basic characteristics:

- 1 1 The ability to place, easily manipulate and angle the imaging transducer within the confines of the limited echocardiographic window.
- 1 2 The ability to display in 2-dimensions and simultaneously record without distortion the motion and position of the rapidly moving cardiac structures.
- 1 3 The ability to freeze motion thus providing a sharp and clear stop motion two-dimensional picture for diagnosis and measurement.

## 2 0 FUNDAMENTALS

Before one can embark on the development of an instrumentation system, two items must be defined. The basic characteristics of the system and the method of achieving these characteristics. The qualities required for a superior two-dimensional real time cardiac imaging system as delineated in section 1 0 shall serve as the systems guideline. The method of choice for this

discussion is pulsed ultrasonic imaging. The best implementation of this method can only be ascertained after an analysis of pulsed ultrasound two-dimensional real time imaging fundamentals.

In order to obtain images by the use of pulsed ultrasonic energy it is required to transmit brief ultra-high frequency acoustics signals forming an ultrasonic beam followed by a relatively long interval during which no transmission occurs. During this time the pulse energy is transmitted through the body. Whenever a pulse of energy strikes a boundary between two surface having different acoustic impedances, a portion of the energy is reflected some of it returning to the source. The remaining portion of the original energy is available to produce additional echos from deeper interfaces. The ultrasonic transducer which serves the purpose of both a transmitter and receiver of acoustic signals converts the ultrasonic energy reflected back from the body into electrical signals as they arrive at the transducer's surface. This signal is amplified, processed and displayed as a single line of ultrasonic information which shows the relative position of tissue interfaces along the axis of the ultrasonic beam. The second dimension of the ultrasonic image which will display the spatial orientation and shape of the body structures is established by rapidly scanning the ultrasonic beam along the surface of the body in either a linear or sector pattern. A separate electrical signal analogous to the instantaneous position of the scanned ultrasonic beam is processed and utilized to create horizontal and vertical signals which are used to direct the motion of the electron beam of a cathode ray tube such that it coincides with the instantaneous position of the returning ultrasonic beam. The resultant image formed from the multi-positioned ultrasonic lines of information is a representation of the internal organs of the body.

It is clear from the above discussion that it takes time to form a two-dimensional ultrasonic image. The time required is dependent upon the speed of sound in body tissue, the depth of body tissue that is to be visualized and the speed at which the ultrasonic beam is scanned across the body.

The velocity of sound utilized by the American Institute of Ultrasound in Medicine for the purpose of aligning, calibrating and measuring the performance of a pulsed echo diagnostic apparatus is 1540 Meters/sec (1). Using this number we find that ultrasound will traverse within the body 1.54 mm every microsecond or in 649 microseconds ultrasound will travel



of his book entitled "Echocardiography" published by Lea & Febiger sound travels poorly through a gaseous medium such as air. It is not possible for ultrasound to traverse any significant amount of lung tissue and still obtain adequate echoes from the heart. The acoustic mismatches between bone and soft tissue is great. If one tries to direct the sonic beam through bone almost all of the ultrasonic energy is reflected or absorbed. Thus an echocardiographic examination is impractical if the transducer is placed over the sternum or rib. This problem may not be as great with infants or young children since the ribs and even sternum may not be calcified. However in adults one is limited as to how the echocardiographic examination is performed with respect to transducer placement. The usual echocardiographic "window" is between the second and fifth intercostal spaces within 3 to 4 cm to the left of the sternal border. One can usually examine the heart from at least two or sometimes three interspaces. In many adult patients the second interspace has lung overlaying the heart and is a difficult location for the echocardiographic examination. In some adults with low diaphragms even the third or fourth interspace might be extremely difficult because of overlaying lung. On the other hand in children the higher interspaces are commonly available for the echocardiographic examination and in young infants the transducer can probably be placed right over the sternum and the ribs if necessary.

These clinical realities are the starting point for the development of the perfect two-dimensional real time echocardiographic imaging system. They indicate that the visualization system of choice will have the following basic characteristics:

1. The ability to place, easily manipulate and angle the imaging transducer within the confines of the limited echocardiographic window.
2. The ability to display in 2-dimensions and simultaneously record without distortion the motion and position of the rapidly moving cardiac structures.
3. The ability to freeze motion thus providing a sharp and clear stop motion two dimensional picture for diagnosis and measurement.

## 2.0 FUNDAMENTALS

Before one can embark on the development of an instrumentation system two items must be defined. The basic characteristics of the system and the method of achieving these characteristics. The qualities required for a superior two-dimensional real-time cardiac imaging system as delineated in section 1.0 shall serve as the systems guideline. The method of choice for this

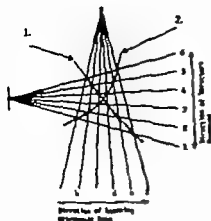


Fig 1 "Moving stick analogy to show distortion. If set due to slow scan rate

1 Shape of displayed structure being visualized by an Ultrasonic imaging system with a slow scan rate relative to the speed of the structure. In this case the structure movement is from top to bottom

2 Shape of displayed structure being visualized by an Ultrasonic imaging system with a slow scan rate relative to the speed of the structure. In this case the structure movement is from bottom to top

In the real time moving image would be that of an artificial flapping of the structure being visualized

Distortions due to finite acquisition time are not the only two-dimensional ultrasonic image aberrations that can occur. It was stated earlier that pulsed ultrasonic energy forms a beam. Since this beam has a finite cross sectional dimension and is composed of ultrasonic energy pulses of finite width the body structures will not be displayed with perfect accuracy. The effect of pulse width is to increase the apparent thickness of a structure. Distortions due to cross sectional beam shape depend on the scanning system employed, the degree of beam divergence, the distance between the transducer face and the structure being visualized, and the intensity of anomalous off-axis beams called side lobes.

Fig 2 is a simplified representation of an ultrasonic scanning system which utilized a linear array transducer. This transducer is composed of many small transducer elements placed side by side. The ultrasonic beam is scanned by firing each one of these transducers sequentially, thus causing each subsequent ultrasonic beam to be displaced laterally from the previous beam.

As the ultrasonic beam propagates away from the face of the transducer elements it remains essentially collimated for a distance determined by the dimensions of the element and the frequency of the transmitted ultrasonic energy. It then begins to diverge. The greater the physical dimensions of the element and the higher the ultrasonic frequency employed, the longer the near field. For a rectangular transducer element the length of the near field in the lateral dimension will not be the same as the length of the near field in the direction orthogonal to the lateral dimension. The need for a large number of lateral scanning positions in a linear array scanning system dictates that the lateral dimensions of the transducer elements used must be

through one millimeter of tissue. In order to sense the presence of a body structure it is necessary for the acoustic pulse to travel to the interface, be reflected and arrive back at the transducer. Therefore it requires 1.298 microseconds to visualize a structure one millimeter away from the transducer face.

At least 15 centimeters of tissue depth must be displayed for the purpose of adult cardiac imaging. This means that each single line of ultrasonic information can be acquired in no less than 194.7 microseconds. If we desire to create a two dimensional picture it is required, as outlined earlier, to scan the ultrasonic beam across the body. The speed at which we scan will determine how many lines of ultrasonic information the final image will contain. The slower the scanning speed, the more ultrasonic lines in the display.

Clearly, the final picture will appear smoother if more ultrasonic lines are used. What is not so evident is that a slow scan of a rapidly moving structure leads to image distortion.

Figure 1 is a simplified representation of a realtime ultrasonic two-dimensional scanning system in the process of imaging a fast moving cardiac structure, such as an aortic valve. No attempt has been made in this illustration to properly represent the actual contours of this complex structure. It is assumed that the valve is pivoted on one end and moves as a stiff stick-like formation. An imaging device which employs a sector type scan has been chosen only for easy of explanation. This discussion applies equally well to a linear scanning system.

As can be seen by the schematic representation in fig. 1, the structure which is being visualized moves during the time that the ultrasound beam is being scanned across its surface. When the scanning beam is in position *a*, the structure is in position 1. At this point in time a dot representing the intersection of the ultrasonic beam and the structure is drawn on the display screen. A short time later a dot representing the intersection of beam position *b* and structure position 2 is drawn on the display screen. This process continues until the ultrasonic beam has finished its scan at beam position *f* and structure position 5. The resultant image is a curved slanted line. If the structure direction was from top to bottom instead of from bottom to top, the resultant image would again be a curved slanted line but it would be oriented at an angle with respect to the first line. The distortion that one would see

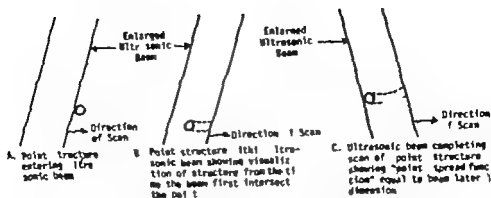
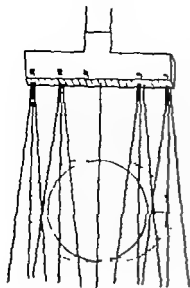


Fig 3 Graphic representation of distortions resulting from beamwidth in a sector scanning imaging system with a collimated beam.

Image uncertainties due to the effect of transducer beam side lobes are most often associated with phased array imaging systems. These anomalous off axis beams caused by the limited number of elements that can be practically used to construct a phased array transducer and the unavoidable edge discontinuities between closely spaced adjacent elements can result in the multiple display of the same structure in different screen locations. Image ambiguities may follow if a strongly reflecting target is at the location of the side lobe while a weakly reflecting target is being visualized by the main lobe (9). This phenomenon is schematically represented in fig 4.

Three beams are illustrated on this simplified representation: one main axis beam and two side lobes. When the main axis beam intersects the strong ultrasonic reflecting structure shown, the processed reflections from the interface will properly display the structure as shown in panel A. At this time the side lobes are not intersecting the formation and therefore only the actual structure is visualized. When side lobe A intersects the structure as shown in panel B, the main axis is pointing to the right. Because the display system is designed to show echoes from the main axis beam only, the received echoes from side lobe A are shown on the right portion of screen. The same is true for side lobe B when it intersects the structure only at this time the main axis beam is pointing towards the left, thus causing echoes from side lobe B to be shown on the left. Panel D shows the composite image resulting from the main beam and the two side lobes. It should be noted that real side lobes are typically wider than the main beam and that the phantom images will therefore be less distinct but smeared over more area than the real image.



*Fig 2 Distortion caused by linear scanning array beam width*

relatively small. This leads to a short near field and a rapidly diverging series of scanned ultrasonic beams. Image distortions due to these spreading beams are schematically represented in fig 2. Points on the circular structure visualized by the off-axis ultrasonic energy intersecting the structure being viewed appear on the ultrasonic image as if they were shifted up or down onto the beam's main axis from their actual positions (5). This leads to an oval representation of the circular structure. In reality this simplified diagram does not indicate all the distortions produced by the diverging ultrasonic beams. Multiple intersections by various portions of the non collimated beam have not been shown

for clarity. It should be noted that it is common practice to fire groups of transducer elements together in an attempt to collimate the beams.

Beam width affects images produced by an ultrasonic visualization device which employs a sector-shaped scan in a different manner than that described for a linear scanning system. In the case of the "mechanical sector scanning system as well as the phased array" scanning system lateral beam dimensions cause individual points on a structure to be mapped into curved lines on the final displayed image. Fig 3 shows this phenomenon graphically.

As the ultrasonic beam passes over the point being visualized an ultrasonic echo is produced. This echo continues to be exhibited for as long as the point is within the confines of the passing ultrasonic beam. The image thus produced will be a curved line which begins when the structure first enters the ultrasonic beam and ends when the lateral dimension of the ultrasonic beam no longer intersects the point. This misrepresentation is minimized for a mechanical sector scanner system by using a transducer of sufficient diameter to allow the existence of a relatively lengthy near field zone and by the use of acoustic lenses in front of the transducer element to further collimate the beam. This will cause the structure to be illuminated by a parallel converging or slowly diverging ultrasonic beam for most of the image depth, thus limiting the image point spread function to approximately the diameter of the transducer element utilized. Some phased array scanning systems utilize electronic focusing means to minimize this problem (8).

higher frequencies result in greater ultrasonic attenuation within the body thus placing a limitation of tissue depth penetration. A practical system must therefore have a relatively large transducer. This large transducer requires an acoustic window which frequently may be larger than is available. With respect to adult cardiac patients this problem is especially true. The transducer will of necessity cross the ribs and in adults these structures are frequently calcified thus causing an image distortion. In addition one does not have the ability to angle the transducer in the long axis (2). Clearly the transducer would lift off the patient's chest causing a loss of image.

For cardiac use the transducer associated with a phased array imaging system does not display the size limitations of the transducer associated with the linear array imaging system. Phased array transducers which are 23 mm in length and 14 mm in width (the width dimension corresponds to the elevation dimension of each of the transducer elements) are in present use (7). However there still remains a problem associated with transducer angulation and acoustic window restrictions. For a phased array transducer to give best results it is necessary for all of the elements of the transducer to be in intimate contact with the patient's chest. The phased array transducer being a rigid structure will lift partially off the skin surface in the process of angling the transducer in the long axis direction. A degraded image will result. In addition because the beams from all of the elements contained within a phased array transducer are required in order to scan or focus the beam any beam obstruction caused by calcified ribs for example will produce image distortions.

At the present time the transducer associated with the mechanical sector scanner imaging system represents the best overall combination of qualities. Because it uses a transducer with a small single ultrasonic element (current models utilize elements which are 12.7 mm in diameter) the mechanical sector scanner probe is easy to place, manipulate and angle within the confines of the echocardiographic window. The small diameter of the ultrasonic element allows unobstructed placement between adult ribs and maintenance of contact with the chest surface during procedures which require transducer angulation. In addition the mechanical system offers a great deal of flexibility with respect to specialized transducer configurations. The transducers most commonly associated with a mechanical sector scanner are ones in which the transducer element oscillates on the skin through an angle of from 30 to 60 degrees. When a transducer with a 30 degree angle is employed the vibratory

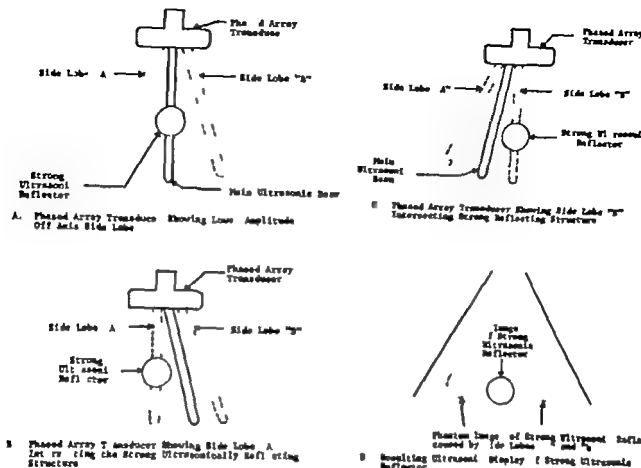


Fig 4 Visualization of a strong ultrasonic reflector by an imaging system with side lobes

### 3.0 THE ECHOCARDIOGRAPHIC TRANSDUCER

After an analysis of two-dimensional real time ultrasonic imaging fundamentals has been completed one can continue to pursue the development of a cardiac imaging system based on this technology. As was pointed out in section 1 one of the three basic characteristics of the cardiac visualization system of choice is that the transducer utilized by the system will be easy to place, manipulate and angle within the confines of the limited echocardiographic window. The transducer associated with the linear array scanning system because of the need to have many transducer elements side by side in order to obtain a sufficient number of ultrasonic lines of information in a linear scanning formation must be in the form of a straight bar. This bar (see fig 2) will vary in size depending on the acceptable ultrasonic line density, distortion, resolution and operating frequency. As pointed out earlier all of these qualities are interrelated. The smaller the transducer element the poorer the resolution and the greater the distortion. The higher the ultrasonic frequency the better the resolution and the less the distortion. However in this case a penalty is paid in that

higher frequencies result in greater ultrasonic attenuation within the body thus placing a limitation of tissue depth penetration. A practical system must therefore have a relatively large transducer. This large transducer requires an acoustic window which frequently may be larger than is available. With respect to adult cardiac patients, this problem is especially true. The transducer will of necessity cross the ribs, and in adults these structures are frequently calcified, thus causing an image distortion. In addition, one does not have the ability to angle the transducer in the long axis (2). Clearly, the transducer would lift off the patient's chest causing a loss of image.

For cardiac use, the transducer associated with a phased array imaging system does not display the size limitations of the transducer associated with the linear array imaging system. Phased array transducers which are 23 mm in length and 14 mm in width (the width dimension corresponds to the elevation dimension of each of the transducer elements) are in present use (7). However, there still remains a problem associated with transducer angulation and acoustic window restrictions. For a phased array transducer to give best results, it is necessary for all of the elements of the transducer to be in intimate contact with the patient's chest. The phased array transducer, being a rigid structure, will lift partially off the skin surface in the process of angling the transducer in the long axis direction. A degraded image will result. In addition, because the beams from all of the elements contained within a phased array transducer are required in order to scan or focus the beam, any beam obstruction caused by calcified ribs, for example, will produce image distortions.

At the present time, the transducer associated with the mechanical sector scanner imaging system represents the best overall combination of qualities. Because it uses a transducer with a small, single ultrasonic element (current models utilize elements which are 12.7 mm in diameter), the mechanical sector scanner probe is easy to place, manipulate, and angle within the confines of the echocardiographic window. The small diameter of the ultrasonic element allows unobstructed placement between adult ribs and maintenance of contact with the chest surface during procedures which require transducer angulation. In addition, the mechanical system offers a great deal of flexibility with respect to specialized transducer configurations. The transducers most commonly associated with a mechanical sector scanner are ones in which the transducer element oscillates on the skin through an angle of from 30 to 60 degrees. When a transducer with a 30 degree angle is employed, the vibratory



sensation on the patient's skin can be made relatively small with proper transducer manipulation. Devices of this nature have been used on neonates which were only several days old, with success (6). As the angle increases however, the vibratory sensation becomes a greater and greater problem.

A hand held mechanical transducer has been suggested which utilizes a rotating transducer element system totally immersed in an acoustically transparent fluid and which is sealed within an acoustically transparent housing (4). This configuration will totally eliminate any vibratory sensation and simultaneously expand the transducer's angle of view to 90 degrees.

#### 4.0 ECHOCARDIOGRAPHIC IMAGE DISPLAY TECHNIQUES

All two dimensional imaging systems, whether they are based on linear scanning, mechanical scanning, or phased array scanning principles, must use electronic display techniques in order to place the ultrasonic image on a screen. There are numerous methods for performing this task. However, the second and third basic requirements of an imaging system, especially designed for cardiac diagnosis, limits our selection. As outlined in section 1, the imaging system of choice will have the ability to display in two-dimensions and simultaneously record without distortion, the motion and position of the rapidly moving cardiac structures. It will also be able to freeze this motion and thus provide a sharp, clear stop motion, two dimensional picture for diagnosis and measurement.

As discussed in section 2, the original data which is used to create an ultrasonic image is in the form of ultrasonic lines of information. These lines of information form an image when they are drawn on a cathode-ray tube screen in synchronism with the instantaneous position of the ultrasonic beam. This is the basic function of an ultrasonic imaging system regardless of the beam scanning mechanism employed. However, if a system is to meet the strict echocardiographic requirements delineated above, the format utilized to draw the ultrasonic lines of information on the cathode ray tube screen must be carefully chosen.

The scanning format utilized must be compatible with the manner in which the ultrasonic beam is being swept across the body. In case of the linear array system, the ultrasonic lines of information are perpendicular to the direction of the scan. Therefore the display format for this type of system would consist of horizontal lines which are drawn on the screen parallel to

one another in the form of a rectangle. For a system which employs a sector scan the lines of ultrasonic information would be distributed in a radial pattern. The format for this system would be composed of lines lying on the radii of a triangular shaped sector. The format however is not completely defined until the field rate, frame rate and interlaced scanning ratio have been determined. These specifications are the ones which effect the system's motion visualization capability the most.

Interlaced scanning is a method of image formation on the screen of a cathode ray tube in which the image is composed of two or more parts laid down sequentially in two or more sets of lines. The first set of lines which forms the first part of the image is drawn on the screen followed by the interlaced placement of one or more additional sets of lines which form the remaining portions of the image. Each individual set of lines is called a field. The composite of all of the image parts which make up the whole image is called a frame. In a non-interlaced scanning system the whole image is formed by one set of scan lines. Therefore a field equals a frame which equals the whole non-interlaced image. Hence the term field has no meaning with respect to this scanning arrangement.

It has been clinically determined that an echocardiographic system which employs an interlaced scanning method with a field rate of 60 fields per second adequately stops cardiac valvular motion in most cases. The faster the field rate the better especially in the case of valvular studies (3). However there is a practical limit to the field rate a system can utilize. By using the time that is required to acquire echo information from a depth of 15 centimeters of tissue which was calculated in section 2, 194.7 microseconds plus the time needed to assure that echos from structures deeper than 15 centimeters are attenuated sufficiently so that they will not mix with the near field echos from the subsequent pulse 65 microseconds and dividing this number into the time that is allotted to draw a crisp cardiac image 16.7 milliseconds

( $\frac{1}{60 \text{ fields per second}}$  16.7 milliseconds per field) it is found that the maximum number of ultrasonic lines that can be displayed in a field which provides adequate valvular motion rendition is 64.3 lines

$\frac{16.7 \text{ milliseconds per field}}{194.7 \text{ microseconds per ultrasonic line} + 65 \text{ microseconds}}$	$64.3 \text{ ultrasonic lines per field}$
--	---

For a non interlaced scanning format the number calculated above indicates that the final image visualized by the viewer will be composed of a maximum of 64 3 ultrasonic lines of data. This is not the case for an interlaced scanning format. Due to the persistence associated with the viewer's vision a frame which is composed of two interlaced fields will appear to have twice this number of ultrasonic data lines or a total of 128 6 lines. Taking this concept further and utilizing a frame composed of four interlaced fields an image will be produced which appears to contain 257 2 ultrasonic data lines.

This technique does more than just fool the eye into believing that the picture on the screen is made up of a great number of lines. It also alters the distortion produced by motion of the cardiac structures. The motion distortion schematically illustrated by fig 1 (the "moving stick analogy") applies to either the fields of an interlaced system or the frames of a non interlaced system. It indicates that attempting to increase the number of ultrasonic data lines in an interlaced field or a non interlaced frame by reducing the transducer's scanning rate will produce a moving image with an artificial flapping artifact. Fig 5 illustrates an interlaced scanning system with a four field to one frame interlacing format and a field rate of 60 fields per second. Field 1 is shown scanning across the structure being visualized in 16 7 milliseconds, a scanning speed which is fast relative to the speed of the structure. This allows the "moving stick" to be shown as a straight line in the display. Field 2 scans at the same rate as field 1, thus the moving stick visualized by field 2 is in a slightly lower position than the moving stick visualized by field 1. The same is true for fields 3 and 4.

Since the ultrasonic image is formed by the echos created by the intersection of the ultrasonic beam and the structure being visualized, the interlaced frame will show a series of points which have been acquired during the total frame time of 66 8 milliseconds (16 7 milliseconds  $\times$  4 = 66 8 milliseconds). The points produced by field 1 will be displaced from the points produced by field 2. The points produced by each field will be displaced from the points produced by the previous field in either an upward or downward direction depending on the direction of the structure being visualized. Fig 5 indicates that a saw tooth image aberration is produced when the structure moves downward. The dots descend until the next ultrasonic line from field 1 is

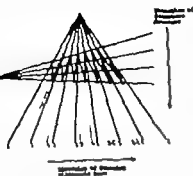


Fig 6: "Moving stick" analogy to show motion artifact caused by an interlaced scanning system with a four field to one frame scanning ratio

drawn and then they reset to the position of the "moving stick" at the time of the field 1 scan. The slower the structure being imaged the smaller the saw tooth distortion. Unlike the bending and flapping image aberrations caused by a field rate which is slow as compared to the speed of the cardiac structures, the sawtooth distortion can be easily seen for what it is, a visualization artifact caused by the imaging system. Thus there can be no doubt as to the true shape of the moving structure. Clearly the capability of distinguishing between artifact and true structure outline plus the ability to create an image with a high line density makes the interlaced scanning method a very attractive display technique for use in an imaging system designed for the study of cardiac pathology.

#### 5.0 ECHOCARDIOGRAPHIC IMAGE RECORDING TECHNIQUES

The need to simultaneously display and record the echocardiographic image immediately leads the designer of a real time ultrasonic imaging system to an analysis of the available means of performing this function. A strong desire to provide a system which allows instant playback of the recorded images focuses the attention of the designer onto the various ways one can use video tape recorders to provide the recording capability. Fig 6 illustrates a technique in which a video tape recorder in conjunction with a television monitor may be used. The ultrasonic image is first formed on the cathode ray tube screen of the "X Y Monitor". This device is under the direct control of the signals which represent the instantaneous position of the ultrasonic beam in both the horizontal (X) and vertical (Y) directions and the signal which represents the amplitude and duration characteristics of the returning echo ("Z"). In front of this monitor is placed a television camera which utilizes a vidicon photoconductive camera tube. A vidicon converts the optical ultrasonic image appearing on the X Y Monitor screen into a television image by the use of an electron beam scanning a photoconductive target placed in the focal plane of the camera's lens. The resultant electronic signals from the television camera which represent the original ultrasonic image can now be displayed on a television monitor or recorded by a video tape recorder. Since the format in which the television image is scanned onto the television monitor's cathode-ray tube screen is entirely different than the

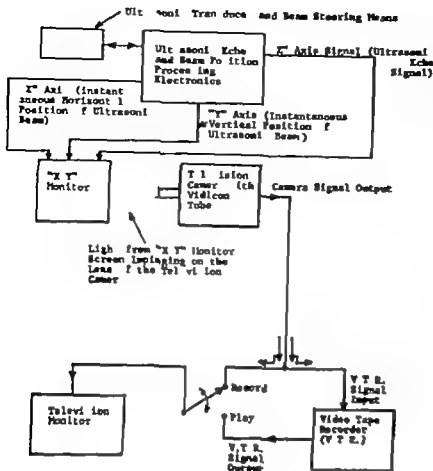


Fig 6 Vidicon scan converter system for simultaneously displaying and recording an ultrasonic image

scanning format as associated with the ultrasonic image this process is called scan conversion

Vidicon scan conversion has the benefit of being very simple to implement with devices that are inexpensive and readily available. It however has some significant drawbacks due

to the nature of the vidicon tube itself and the characteristics the system must possess to be able to perform the scan conversion function. In order to properly act as a scan converter the vidicon's photoconductive target must have the ability to retain the electrical impression of the image being viewed the ultrasonic image for the time required to scan this image on the X-Y Monitor's screen plus the time required to scan one television field. Fig 7 shows this graphically. Panel A shows the relative position between the television scan line and the ultrasonic data line at the start of the scan conversion process. At the instant in time illustrated the television scan line has traversed the entire horizontal width of the vidicon's target while the ultrasonic data line has traveled from its origin the apex of a triangular shaped sector in this example to the equivalent of approximately 4 centimeters of body tissue. It can be seen from the schematic representation that the T-V scan line intersects the ultrasonic line of data in only one place. This occurs because of the radically different scan rates and scan directions associated with the two display systems. Panel B depicts the situation that exists approximately a millisecond after the scan conversion has been initiated. Lines that have already been scanned appear as dashed lines. The resulting television image will be composed of the intersections between the tele

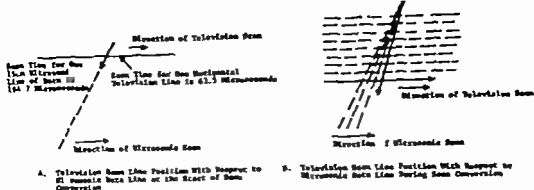


Fig 7: The operation of a vidicon scan converter

vision scan lines and the scan line which comprise the optical ultrasonic image. If there was no mechanism to maintain the electrical impression of the optical image on the vidicon's photoconductive target, the intersection of the television scan lines and the ultrasonic image scan lines would seldom occur because by the time the television scan lines reach the bottom of the photoconductive target (this requires 16.7 milliseconds in the NTSC television system used in the United States) the scan lines associated with the earlier portions of the optical ultrasonic image would no longer be available. Thus no television image would be formed. There are two ways to overcome this difficulty. The first way would be to use an X-Y monitor that utilizes a cathode-ray tube with a long persistence phosphor. This would have the effect of retaining the optical image on the monitor screen for a long enough period of time to assure that proper scan conversion occurs. The second method would be to use a vidicon tube which employs a photoconductive target with the appropriate image retention characteristics.

It must be noted that the persistence associated with the scan conversion process will alter the final appearance of the echocardiographic image displayed on the television monitor. This is due to the fact that once the optical image is scanned by the television scanning system, no mechanism exists to immediately erase this temporarily stored image. Instead, the image fades away over a period of time determined by vidicon and cathode ray tube characteristics. Thus the following ultrasonic field or frame will overwrite on top of the earlier image. (In actuality it may require three to five television frames for the first ultrasonic image to fade to the point at which it can no longer be seen.) Each individual television image therefore contains "history" from previous ultrasonic events.

When the television image is recorded either by a photographic method or by the use of a video tape recorder, the history artifact is also recorded. The

resulting image therefore presents cardiac structures which are ill defined due to position uncertainties. In addition to this aberration the non uniform manner in which past cardiac images fade causes single field television images like those obtained when the image from a video tape recorder is frozen by stopping the forward motion of the video tape to appear unevenly illuminated. Clearly the longer the vidicon scan convertor's persistence characteristic the worse the history artifact and the better the uniformity of illumination associated with the final stopped two dimensional cardiac image.

Another means for simultaneously displaying and recording the echocardiographic image is shown in fig 8. The system illustrated is referred to as the direct ultrasonic recording and display method. This name is appropriate because the electronic signals associated with the echocardiographic image are displayed and recorded without use of a scan convertor. Therefore the image visualized is always a direct reproduction of the original cardiac imaging signals. As is the case for the vidicon scan conversion technique the echocardiographic image is first displayed on the screen of an X-Y monitor. However in this system much care is taken to assure that the X-Y image format can be time synchronized with a television image format. This means that the ultrasonic imaging system is designed such that each ultrasonic field is scanned in 16.7 milliseconds. Thus by the use of the appropriate electronic configuration the ultrasonic imaging system can be synchronized with a standard video tape recorder thereby allowing the original ultrasonic signals to be recorded onto video tape. Under these circumstances the X-Y monitor serves only as a means to view the echocardiographic image before and after recording.

There are two significant benefits associated with the direct ultrasonic display and recording approach. The first is that the recorded and displayed echocardiographic images are free of artifacts produced by necessary system persistence. On the surface this statement seems to require no further explanation. In fact however it has some non obvious implications. Since the displayed and recorded images are always composed of original ultrasonic data the amount of history artifact is only a function of the type of phosphor used in the cathode ray tube of the X-Y monitor used to display the image. In addition if a frozen image is displayed by stopping the forward motion of a video tape that had been previously recorded the image being viewed will be totally free of history artifact and be evenly illuminated over the entire area of the image. This is true regardless of the type of

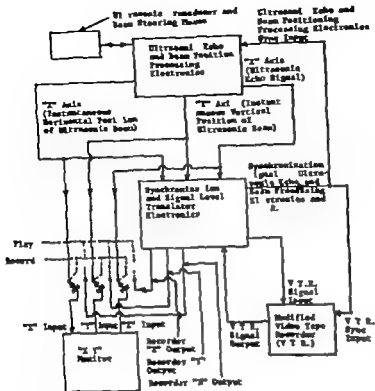


Fig 8: Direct ultrasonic recording and display system.

phosphor used in the X Y monitor. The reason for this stems from the fact that a video tape recorder utilizes a rotating record-playback head that will play back a complete single field of ultrasonic information when the forward tape motion is halted. Since there is no history artifact or fading associated with the original ultrasonic data and these aberrations are caused either by previous ultrasonic fields being overwritten onto the field currently being displayed or the ultrasonic field fading before complete scan conversion takes place, the frozen single field image being shown will be free of these artifacts.

The second benefit is the ability to record a full 15 centimeter tissue depth ultrasonic image and play back this image with any desired tissue depth up to 15 centimeters. This capability is derived from the fact that the original ultrasonic image signals are available at the time the recorded echocardiographic images are played back, thus allowing a change in the tissue depth displayed by simply changing the electronic sweep rate associated with the depth-dimension of the X Y monitor. Since a system which utilizes a scan conversion process does not allow the retrieval of the original ultrasonic data, it cannot readily provide this feature.



## 6 CONCLUSIONS

It was the purpose of this discussion to analyze the principles of two-dimensional real time echocardiographic imaging and from this analysis develop the system ideally suited for the performance of this function. In general it has been shown that a mechanical sector scanner which ultrasonically scans the surface of the chest in 16.7 milliseconds in conjunction with a direct ultrasonic display and recording system, presently represents the real time cardiac imaging device that comes closest to fulfilling all of the clinical requirements. This conclusion is based on the fact that the combination of elements described above utilizes the smallest echocardiographic window; provides the least amount of image distortions and ambiguities and provides clear uniformly illuminated two-dimensional stop motion images which do not display a "history artifact".

## REFERENCES

- 1 ERIKSSON K R Diagnostic ultrasound standardization in North America. Proceedings of the second European conference on ultrasound in medicine, Munich May 12 - 16, 1975
- 2 FEIGENBAUM H Echocardiography Second Edition Lea and Febiger Philadelphia Pennsylvania 1976
- 3 FEIGENBAUM H M D Professor of Medicine Director of Hemodynamic Laboratories Indiana University School of Medicine Senior Research Associate Krannert Institute of Cardiology Indianapolis Indiana Personal communication
- 4 GOLDBERG M R Ultrasonic scanning system and method United States Patent Pending assigned to Smith Kline Instruments Sunnyvale California
- 5 ROELANDT J VAN DORP W G BOM N LAIRD J D and HUGENHOLTZ P G Resolution problems in echocardiography A source of interpretation errors Amer J of Cardiol 37 256, 1976
- 6 SAHN DAVID J M D Assistant Professor of Pediatrics (Cardiology) The University of Arizona Arizona Medical Center Tucson Arizona Personal communication
- 7 VON RAMM O T and THURSTONE F L THAUMASCAN Design considerations and performance characteristics Ultrasound in Medicine volume 1 Proceedings of the 19th annual meeting of the American Institute of Ultrasound in Medicine Plenum Press New York and London 1975
- 8 VON RAMM SMITH S W and THURSTONE F L Gray Scale Imaging with Complex TCG and transducer arrays Proceedings of the Society of Photo-Optical Instrumentation Engineers vol 70 Application of Optical Instrumentation in Medicine IV Sept 25 27 1975 Copyright 1975
- 9 VON RAMM O T THURSTONE F L and THAUMASCAN Design considerations and performance characteristics Ultrasound in Medicine volume 1 Proceedings of the 19th Annual Meeting of the American Institute of Ultrasound in Medicine Plenum Press New York and London 1975

# THE CROSS-SECTIONAL ECHOCARDIOGRAM IN CLINICAL CARDIOLOGY APPLICATIONS AND RELATIONSHIP TO THE M-MODE TECHNIQUE

A E WEYMAN

*From the Krayer Institute of Cardiology the Department of Medicine  
Indiana University School of Medicine and the Veterans Administration  
Hospital Indianapolis Indiana*

## SUMMARY

Until recently M-mode echocardiography has been the standard in clinical practice. Although the M-mode systems provide rapidly acquired high resolution data concerning regional cardiac interface position and motion, the limited area encompassed by the narrow M-mode beam and failure to provide spatial orientation may be a significant limitation in selected clinical areas.

Cross-sectional echocardiography expands the area of the heart which is available for study and displays the acoustic images in a dynamic spatially oriented format allowing the moving cross-sectional anatomy of the heart to be visualized. This variation in method of display provides more extensive information concerning valvular heart disease by permitting analysis of the morphology and motion patterns of the cardiac valves, direct visualization of valvular orifices, and appreciation of valvular movement in relationship to surrounding cardiac chambers. In patients with ischemic heart disease the cross-sectional systems increase the area of the ventricle which is available for ultrasonic study by adding the cardiac apex and the medial and lateral walls of the ventricle to the recorded data. In addition the systems permit localized distortion in left ventricular shape and function to be evaluated. Finally, in congenital heart disease the cross-sectional systems permit the orientation of the great vessels and cardiac chambers to be determined. In this report we have presented examples of the applications of cross sectional echocardiography in each of these areas in the hope that the reader can gain from these isolated examples an overall appreciation of the potential of this type of instrumentation and its relationship to the more conventional M-mode display.

---

## 6 D CONCLUSIONS

It was the purpose of this discussion to analyze the principles of two dimensional real time echocardiographic imaging and from this analysis develop the system ideally suited for the performance of this function. In general it has been shown that a mechanical sector scanner which ultrasonically scans the surface of the chest in 16.7 milliseconds in conjunction with a direct ultrasonic display and recording system presently represents the real time cardiac imaging device that comes closest to fulfilling all of the clinical requirements. This conclusion is based on the fact that the combination of elements described above utilizes the smallest echocardiographic window, provides the least amount of image distortions and ambiguities and provides clear uniformly illuminated two-dimensional stop motion images which do not display a history artifact.

## REFERENCES

- 1 ERIKSSON K R Diagnostic ultrasound standardization in North America. Proceedings of the second european conference on ultrasound in medicine Munich May 12 - 16 1975
- 2 FEIGENBAUM H Echocardiography Second Edition Lea and Febiger Philadelphia Pennsylvania 1976
- 3 FEIGENBAUM H M D Professor of Medicine Director of Hemodynamic Laboratories Indiana University School of Medicine Senior Research Associate Krannert Institute of Cardiology Indianapolis Indiana Personal communication
- 4 GOLDBERG P R Ultrasonic scanning system and method United States Patent Pending assigned to Smith Kline Instruments Sunnyvale California
- 5 ROELANDT J VAN DORP W G BOM N LAIRD J D and HUGENHOLTZ P G Resolution problems in echocardiography A source of interpretation errors Amer J of Cardiol 37 256s 1976
- 6 SAHN DAVID J M D Assistant Professor of Pediatrics (Cardiology) The University of Arizona Arizona Medical Center Tucson Arizona Personal communication
- 7 VON RAMM O T and THURSTONE F L THAUMASCAN Design considerations and performance characteristics Ultrasound in Medicine volume 1 Proceedings of the 19th annual meeting of the American Institute of Ultrasound in Medicine Plenum Press New York and London 1975
- 8 VON RAMM SMITH S W and THURSTONE F L Gray Scale Imaging with Complex TCG and transducer arrays Proceedings of the Society of Photo Optical Instrumentation Engineers vol 70 Application of Optical Instrumentation in Medicine IV Sept 25-27 1975 Copyright 1975
- 9 VON RAMM O T THURSTONE F L and THAUMASCAN Design considerations and performance characteristics Ultrasound in Medicine volume 1 Proceedings of the 19th Annual Meeting of the American Institute of Ultrasound in Medicine Plenum Press New York and London 1975

Although the cross-sectional systems have only recently become available for clinical trial preliminary data already suggests that the enlarged field of vision and spatial orientation they provide will markedly enhance the diagnostic potential of cardiac ultrasound. In this discussion specific applications of cross sectional echocardiography in valvular ischemic and congenital heart disease will be described. It is hoped by these individual examples to illustrate both the general types of information these systems can provide as well as the relationship of cross sectional and M-mode echocardiography.

## 1 VALVULAR HEART DISEASE

### a Visualization of A-V Valve Morphology Mitral Valve Orifice Size

The observation by Edler that the motion pattern of the echo from the anterior mitral leaflet differed in patients with mitral stenosis when compared to normals represents the initial clinical application of echocardiography (8-9). Since this observation the diagnosis of mitral stenosis has remained the keystone of clinical echocardiography. Although there have been refinements in the M-mode diagnosis of mitral stenosis the original methods for quantitation of severity based on the relative decrease in the initial diastolic closing or E-F slope remain unchanged. Fig 1 is a typical M-mode recording from a patient with mitral stenosis illustrating the characteristic changes in leaflet motion including the reduced diastolic or E-F slope. Although the E-F slope clearly reflects the distending pressure or pressure gradient to which the anterior leaflet is subject during diastole it is also affected by factors other than mitral valve orifice size such as a) the severity of fibrosis or calcification of the leaflet b) the compliance of the ventricle c) the rate of flow through the mitral valve orifice and d) the diastolic motion of the posterior ventricular wall to which the leaflet is attached. Not surprisingly therefore it has recently been shown that attempts to assess the severity of the stenotic lesion using this slope may be misleading in individual cases (10).

The ideal method for evaluating mitral stenosis would be to directly visualize the stenotic mitral valve orifice which is the critical determinant of severity. In 1974 Henry et al. using a prototype mechanical sector scanner demonstrated that direct visualization of the mitral valve orifice was indeed possible with the cross sectional technique (11). These authors observed an excellent correlation between the mitral valve orifice size measured from the cross sectional echogram and the directly measured mitral valve orifice

## INTRODUCTION

The use of pulsed reflected ultrasound as a means of visualizing intracardiac structures is now well established (1 2) Until recently the M-mode echocardiogram has been the standard in clinical practice (3) The M-mode display permits recording of both the depth and motion patterns of intracardiac reflective interfaces relative to a fixed spatial reference and time The high resolution and rapid sampling rate of the M-mode system makes it an ideal method for studying an organ whose component parts display rapid and complex motion such as the heart The M-mode echocardiogram is limited however in that it only provides information concerning the relative position and motion of structures along the narrow path of the ultrasonic beam Thus with the transducer held stationary a very limited area of the heart is visualized at any given time In many areas of cardiac diagnosis such as congenital and ischemic disease the spatial or lateral relationships of cardiac structures or areas of segmental dysfunction may be more important than distance and motion pattern along the beam axis

The initial attempts to add spatial orientation to the M-mode echogram led to the development of M-mode scanning techniques (4) Using an M-mode scan it is possible by sweeping the transducer from one area of the heart to another while continuously recording to derive some information concerning the spatial relationships of the structures examined Unfortunately these scans vary with the speed and path of transducer movement and hence are qualitative at best In addition since both direction and speed of transducer angulation will vary from sweep to sweep and from examination to examination the reproducibility of these data is limited

The continued need for more quantitative spatial information concerning cardiac structure and function led to the development of the two-dimensional or cross sectional echocardiographic systems (5 7) With these systems the beam of ultrasound is either mechanically or electronically swept through a predetermined path while the relative position of the beam in space is continuously recorded In this manner the individual lines of acoustic data can be displayed in an appropriate spatial relationship to one another and as a result the cardiac structures which they reflect visualized in a correct spatially oriented format In addition by rapidly sweeping the beam of ultrasound across the field of examination (i.e. faster than the flicker vision of the eye) dynamic motion can be added to the cross sectional display While the cross sectional techniques does not provide new acoustic data the method of display permits information to be appreciated and utilized which was heretofore meaningless in the absence of a spatial reference

correlation ( $r = 0.95$ ) between the echocardiographic measurement of mitral valve orifice size and the hemodynamic estimate of mitral valve area (12). In a group of 40 patients examined in this laboratory with both isolated stenosis and stenosis with insufficiency a similar correlation was obtained ( $r = 0.90$ ) (13). Fig 2 is a cross-sectional echogram corresponding to the M-mode recording in fig 1. In the left hand panel the mitral valve orifice is directly imaged during diastole. The measured valve area of  $1.3 \text{ cm}^2$  compared with a valve area of  $1.2 \text{ cm}^2$  determined at cardiac catheterization.

These data collected from three separate centers using independently developed imaging systems suggests that cross sectional echocardiography is a valid non-invasive method for direct visualization of mitral valve orifice size is applicable in approximately 90% of patients and correlates with pathologic and hemodynamic determination of mitral valve area.

### B. Semilunar Valve Morphology and Motion Patterns

The evaluation of semilunar valve motion and detection of stenosis is another area where cross-sectional echocardiography has been of particular value. While direct visualization of the valve orifices has proven difficult, examination of the long axis morphology and motion patterns of these valves has permitted detection of stenosis, appreciation of leaflet separation and in some cases estimation of severity (14, 15). In this section we will examine the relative merits of the M-mode and cross sectional system in examining patients with valvular pulmonary stenosis. Patterns of aortic valve motion are similar and will be discussed later in this symposium in the section on left ventricular outflow obstruction.

The M-mode diagnosis of valvular pulmonary stenosis rests on the observed effects of altered right ventricular and pulmonary artery pressure relationships on pulmonary leaflet motion (16). Patients with valvular pulmonary stenosis frequently have a decrease in right ventricular compliance and increased force of right atrial contraction which in the face of normal or low pulmonary artery pressure results in a positive pressure gradient across the valve at end diastole. This pressure gradient produces an opening or doming motion of the valve leaflets following atrial contraction which is reflected by an increase in the normal posterior deflection of the posterior pulmonary leaflet following atrial contraction (A wave depth) (fig 3).

Unfortunately the diagnostic value of these observations is limited by 1) technical difficulty in recording the pulmonary valve, 2) the indirect nature of the derived data, 3) lack of specificity of the hemodynamic abnormalities.

area at surgery or from pathologic specimens. In 13 of their 14 patients the echocardiographic orifice size was within  $0.3 \text{ cm}^2$  of the directly measured mitral valve area. In a subsequent study Nichol et al were able to record the mitral valve orifice in 25 of 30 patients undergoing cardiac catheterization for isolated mitral stenosis and observed an equally excellent

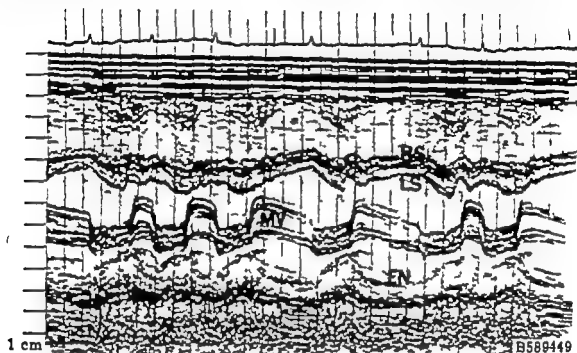


Fig 1 M-mode echocardiogram from the patient with mitral stenosis demonstrating the typical echocardiographic features of the stenotic mitral valve. There is an increase in echo production from the diseased anterior and posterior leaflets, decrease in opening amplitude of the anterior leaflet, anterior motion of the posterior leaflet during diastole, and a decrease in the diastolic or E to F slope. RS = right side of the interventricular septum, LS = left side of the interventricular septum, NV = mitral valve, EN = posterior wall endocardium.

SHORT AXIS CROSS-SECTION OF STENOTIC MITRAL VALVE  
IN SYSTOL (SV) AND DIASTOL (NVO)



DIASTOL

SYSTOL

Fig 2 Short axis cross-sectional scan recorded with the plane of the cross-sectional scan oriented parallel to or directly across the mitral valve orifice. The left hand panel is recorded during diastole and illustrates the thickened fibrotic mitral commissures with a decrease in effective mitral valve orifice area (NVO = mitral valve orifice). The right hand panel recorded during systole illustrates the closed systolic configuration of the mitral valve (NV). The echocardiographic mitral valve orifice in this case measured  $1.3 \text{ cm}^2$  compared to a mitral valve area calculated at cardiac catheterization of  $1.2 \text{ cm}^2$ .

correlation ( $r = 0.95$ ) between the echocardiographic measurement of mitral valve orifice size and the hemodynamic estimate of mitral valve area (12). In a group of 40 patients examined in this laboratory with both isolated stenosis and stenosis with insufficiency a similar correlation was obtained ( $r = 0.90$ ) (13). Fig 2 is a cross sectional echogram corresponding to the M mode recording in fig 1. In the left hand panel the mitral valve orifice is directly imaged during diastole. The measured valve area of  $1.3 \text{ cm}^2$  compared with a valve area of  $1.2 \text{ cm}^2$  determined at cardiac catheterization.

These data collected from three separate centers using independently developed imaging systems suggests that cross sectional echocardiography is a valid non-invasive method for direct visualization of mitral valve orifice size is applicable in approximately 90% of patients and correlates with pathologic and hemodynamic determination of mitral valve area.

### B. Semilunar Valve Morphology and Motion Patterns

The evaluation of semilunar valve motion and detection of stenosis is another area where cross-sectional echocardiography has been of particular value. While direct visualization of the valve orifices has proven difficult, examination of the long axis morphology and motion patterns of these valves has permitted detection of stenosis, appreciation of leaflet separation, and in some cases estimation of severity (14, 15). In this section we will examine the relative merits of the M-mode and cross sectional system in examining patients with valvular pulmonary stenosis. Patterns of aortic valve motion are similar and will be discussed later in this symposium in the section on left ventricular outflow obstruction.

The M-mode diagnosis of valvular pulmonary stenosis rests on the observed effects of altered right ventricular and pulmonary artery pressure relationships on pulmonary leaflet motion (16). Patients with valvular pulmonary stenosis frequently have a decrease in right ventricular compliance and increased force of right atrial contraction which in the face of normal or low pulmonary artery pressure results in a positive pressure gradient across the valve at end diastole. This pressure gradient produces an opening or doming motion of the valve leaflets following atrial contraction which is reflected by an increase in the normal posterior deflection of the posterior pulmonary leaflet following atrial contraction (A wave depth) (fig 3).

Unfortunately the diagnostic value of these observations is limited by 1) technical difficulty in recording the pulmonary valve, 2) the indirect nature of the derived data, 3) lack of specificity of the hemodynamic abnormality



area at surgery or from pathologic specimens. In 13 of their 14 patients the echocardiographic orifice size was within  $0.3 \text{ cm}^2$  of the directly measured mitral valve area. In a subsequent study Nichol et al were able to record the mitral valve orifice in 25 of 30 patients undergoing cardiac catheterization for isolated mitral stenosis and observed an equally excellent

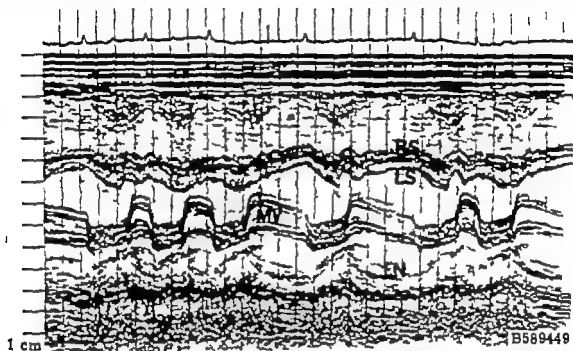


Fig 1 M-mode echocardiogram from the patient with mitral stenosis demonstrating the typical echocardiographic features of the stenotic mitral valve. There is an increase in echo production from the diseased anterior and posterior leaflets, decrease in opening amplitude of the anterior leaflet, anterior motion of the posterior leaflet during diastole, and a decrease in the diastolic or E to F slope. RS = right side of the interventricular septum, LS = left side of the interventricular septum, MV = mitral valve, EN = posterior wall endocardium.

SHORT AXIS CROSS-SECTION OF STENOTIC MITRAL VALVE IN SYSTOLE (MV) AND DIASTOLE (MVO)



DIASTOLE

SYSTOLE

Fig 2 Short axis cross-sectional scans recorded with the plane of the cross-sectional scan oriented parallel to or directly across the mitral valve orifice. The left hand panel is recorded during diastole and illustrates the thickened fibrotic mitral commissures with a decrease in effective mitral valve orifice area. MVO = mitral valve orifice. The right hand panel recorded during systole illustrates the closed systolic configuration of the mitral valve (MV). The echocardiographic mitral valve orifice in this case measured  $1.3 \text{ cm}^2$  compared to a mitral valve area calculated at cardiac catheterization of  $1.2 \text{ cm}^2$ .

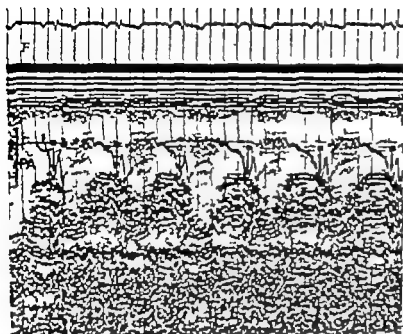
and 4) the general failure of these changes to occur in patients with mild stenosis (17)

The cross sectional technique simplifies the diagnosis of valvular pulmonary stenosis in several ways (18). First the enlarged field of vision provided by this technique facilitates location and recording of the pulmonary artery and valve. Secondly the ability to view the entire domed stenotic valve during systole permits direct determination of stenosis in patients with mild as well as severe obstruction. Fig 4 is a cross-sectional recording of a normal pulmonary valve illustrating the normal systolic position of the fully opened pulmonary leaflets lying parallel and in close proximity to the anterior and posterior margins of the pulmonary artery. In contrast fig 5 is a recording from a patient with moderately severe valvular pulmonary stenosis. In this case the pulmonary leaflets arc inward toward the center of the lumen of the pulmonary artery markedly reducing the separation between the leaflet echoes at the valve orifice. In a series of 22 patients with valvular pulmonary stenosis examined in this laboratory we were successful in recording the pulmonary valve in 20 cases (18). In each case in which the valve was recorded the characteristic systolic doming of the leaflets was evident. In each of 7 patients with mild pulmonary stenosis and normal A waves on the M-mode record systolic doming of the valve was observed on the cross sectional recording. These observations suggest that the cross sectional technique should offer a more sensitive and specific method for evaluating the presence of pulmonary valve morphology and detecting valvular pulmonary stenosis.

### C. Motion of Cardiac Valves in Relation to Surrounding Structures    Mitral Valve Prolapse

In addition to direct visualization of the diastolic mitral valve orifice and the systolic configuration of the stenotic semilunar valves the cross-sectional systems also permit examination of the motion patterns of the cardiac valves in relation to their supporting structures and contiguous cardiac chambers. This is particularly important when attempting to diagnose the mitral valve prolapse syndrome.

The initial observations by Dillon et al (19) and Kerber et al (20) of prominent mid systolic posterior displacement of the mitral leaflets during systole in patients with mitral valve prolapse suggested that M-mode echocardiography might offer a simple reliable non-invasive method for objectively defining the presence of this abnormality. Following these observations however difficulties in appropriately recording the abnormal leaflet motion and defining objective criteria for the diagnosis of prolapse have arisen (21, 22).



Y186397

both phases of the respiratory cycle are consistent with moderate to severe disease (From Weyman A E Pulmonary Valve Echo Motion in Clinical Practice *Amer J Med* 62 843 1977)

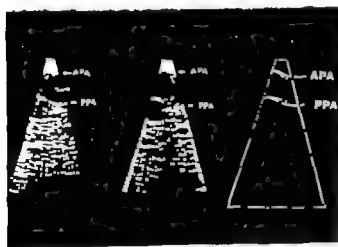


Fig 4 Cross-sectional echogram recorded with the scan plane oriented parallel to the long axis of the pulmonary artery in a normal patient. The left hand panel (Panel A) is recorded during diastole and illustrates the coapted pulmonary leaflets lying in the center of the pulmonary artery (horizontal arrow). The middle panel (Panel B) is recorded during systole. In this panel the pulmonary leaflet lie in a fully open position parallel to the margins of the anterior and posterior surfaces of the pulmonary artery (vertical arrows). The right hand panel (Panel C) is a line drawing corresponding to Panel B.

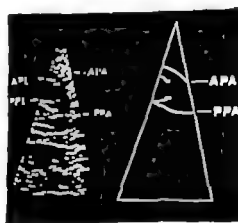


Fig 5 Cross-sectional recording from a patient with valvular pulmonary stenosis demonstrating the characteristic configuration of the stenotic pulmonary valve. The anterior and posterior pulmonary leaflets of the closed valve curve into the lumen of the pulmonary artery reducing the valve orifice and producing restriction to right ventricular outflow.

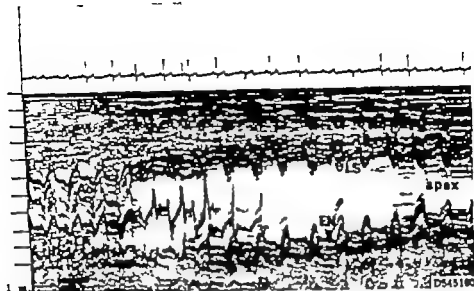


Fig 6 M-mode echocardiographic scan of the left ventricle from the area of the aortic root and left atrium (on the left) through the mitral valve to the cardiac apex (right hand portion of the scan). This scan illustrates the normal contraction sequence of the left ventricle as well as providing a general concept of the shape of the left ventricular chamber.

state remains to be defined. Further preliminary data suggest that the expression of complications of mitral prolapse such as the presence of ectopic beats and ventricular tachycardia does not correlate with the severity of the anatomic derangement. Despite these difficulties the cross sectional echogram should represent an ideal method for visualizing the mitral valve leaflets in patients with mitral valve prolapse syndrome and hence increase our knowledge in this area.

## 11 ISCHEMIC HEART DISEASE

### A. Left Ventricular Structure and Function

Probably nowhere else are the strengths and the weaknesses of the M-mode techniques as apparent as in the study of the left ventricle (25). Fig 6 is a typical M-mode scan of the left ventricle beginning at the aorta and left atrium and continuing through the cavity of the ventricle into the region of the cardiac apex. The high resolution of the M-mode system clearly displays the endocardial and epicardial surfaces permitting determination of left ventricular wall thickness and thickening with systolic contraction while the rapid sampling rate permits detailed definition of the motion patterns of these interfaces relative to time. In addition the scanning technique conveys an impression of overall left ventricular shape. Combining these features provides valuable information

Since mitral valve prolapse may be associated with a number of major complications such as sudden death, intractable congestive heart failure, recurrent ventricular tachyarrhythmias, and bacterial endocarditis, it is highly important if possible to clearly define the patient group with this disorder.

Studies to date using the cross-sectional technique have already helped to clarify many of the problems which have arisen during M-mode study. It was initially recognized by Sahn et al (23) that the prolapsing mitral leaflets move superiorly away from the left ventricle into the cavity of the left atrium rather than posteriorly as suggested by the M-mode record. The path of motion of the prolapsing leaflets is therefore perpendicular to the M-mode beam in many cases causing leaflet motion to be poorly recorded. In addition the normal motion of the left ventricle during systole is anterior and inferior while the motion of the prolapsing leaflets is in the opposite superior and posterior direction. If the magnitude of these vectors is comparable then the spatial motion of prolapsing leaflets may be negligible and hence poorly appreciated. Finally, when visualizing the mitral leaflets with the M-mode echocardiogram, one can only detect motion relative to a fixed reference point. If the transducer is placed superior to the mitral valve, therefore the normal inferior motion of the mitral ring during ventricular systole will result in the mitral leaflets moving away from the transducer or posteriorly on the M-mode record. This may lead to an inappropriate diagnosis of mitral valve prolapse.

The cross sectional technique in contrast permits the leaflets to be visualized throughout the cardiac cycle in their proper spatial position. With this type of visualization it is possible to see both systolic and diastolic motion of the leaflets in relation to the entire mitral valve apparatus and to relate the amplitude of superior motion of the mitral leaflets to the remainder of the left ventricle and left atrial cavity (24). It is also possible to record leaflet motion during periods of induced physiologic stress, such as increase in afterload, change in patient position, maneuvers to decrease left ventricular volume, and administration of pharmacological agents, all of which change the relative size of the left ventricular cavity and affect the degree of prolapse. Studies to date using the cross sectional systems have demonstrated a clear difference in the motion pattern of the mitral valve in patients with classic mitral valve prolapse when compared to normals (24). It appears unfortunately that there is a wide spectrum of mitral leaflet motion varying from very minimal backward or superior motion of the leaflets during systole to unequivocal prolapse. The point at which motion of the mitral leaflet toward the left atrium ceases to be a normal variant and represents a pathologic



Fig 7: Cross-sectional echocardiogram of the cardiac apex. The apical endocardium (EN) as well as the epicardial (EP) surface in the region of the cardiac apex can be visualized. The line drawing to the right of the figure illustrates the normal contraction sequence of the apex.

of regional dysfunction to be appreciated. These topics will be discussed in greater detail in the section on the evaluation of the ischemic ventricle by cross sectional echocardiography later in this symposium.

### III CONGENITAL HEART DISEASE VENTRICULAR SITUS AND GREAT VESSEL ORIENTATION

In the evaluation of congenital heart disease, determination of the location and relative position of the great vessels and cardiac chambers is of paramount importance. Abnormalities of great vessel orientation or transposition of the great vessels represents the commonest form of cyanotic congenital heart disease in newborns (26). Prior M-mode observations suggested that the diagnosis of d transposition could be inferred by recording two parallel great vessels one on top of the other with simultaneous recording of the semilunar valves (fig 8) (27). As previously noted in other sections, however, attempts to establish spatial relationships from the limited area of the heart visualized by the M-mode technique may be misleading. Thus it was subsequently noted that in young children especially if the transducer was placed higher than usual on the chest the close proximity of the AV valves made it possible to record these structures simultaneously giving an appearance similar to that seen with transposition (28). In addition if the heart is shifted rightward due to a malformation of the lungs or thoracic cage a similar picture can be obtained. Thus while in the majority of cases the M-mode technique is a useful means for detecting the presence of transposition in individual instances, these data may be misleading.

In a recent report Henry et al described a method for differentiating anomalies of the great vessels using the cross sectional system (29). Their observations based on necropsy studies indicate that three basic relationships exist between the great arteries as they exit the heart. Normally the two great vessels cross at their origin with the right ventricular outflow tract and pulmonary artery passing diagonally above the aorta. In contrast with transposition complexes the two great vessels leave the heart parallel to one another.

concerning cardiac structure and function in the areas examined. Further the format in which the M-mode display is recorded is very convenient for data acquisition and analysis.

As previously noted, however, the limited area of the left ventricle transected by the M-mode beam represents a significant limitation in assessing left ventricular structure and function in the segmentally diseased ventricle. In this regard a consideration of the data not presented in fig 6 is important. First, as the scan approaches the cardiac apex, the echoes from the anterior and posterior endocardial surfaces abruptly cease. This is characteristic of these scans and occurs because the apex lies relatively parallel to the path of the ultrasonic beam and therefore is not an appropriate reflector, making M-mode recording of this area difficult. In addition, the scan visualizes only a single slice of the beam through the ventricle. The remaining semicircular medial and lateral walls, which comprise the majority of the left ventricular muscle mass, are not included. Thus the non visualized area of the ventricle is larger than that which is recorded, and in patients with segmental disease may be of greater diagnostic significance.

Cross sectional echocardiography is an important adjunct in the evaluation of the left ventricle in a number of areas. First, the spatially oriented display permits the medial and lateral walls of the left ventricle as well as the cardiac apex to be included in the echocardiographic images. Secondly, it allows lateral and oblique as well as axial motion to be recorded. Lateral motion across the beam could not be quantitated with the M-mode technique and was merely reflected as presence or absence of echo production. With the cross sectional display, as a wall or structure moves across the plane of the scan, its echoes will cross one spatially oriented line of acoustic data after another, allowing its lateral motion to be tracked and recorded. One can therefore record lateral motion by following the moving echo from line to line across the scan, axial motion by movement of the echo relative to the transducer, and oblique motion by a combination of the two. Fig 7 is a recording of a long axis of the cardiac apex using the cross sectional system. In this figure, the motion pattern of the cardiac apex from left to right across the plane of the scan, the inward contraction of the anterior and posterior walls, and thickening of the ventricular myocardium during systole are evident. By rotating the transducer  $90^\circ$  to record a short axis of the ventricle, similar information concerning the medial and lateral walls can be obtained. Thus, by permitting visualization of the spatial geometry and motion pattern of the left ventricle, the cross sectional system increases the area of the ventricle which can be examined and permits distortion in left ventricular shape as well as the location and extent



*Fig 9 Short axis cross-sectional scan of the pulmonary artery and aorta. The lateral half of the relatively circular aorta is visualized to the right while the half moon or sausage shaped pulmonary artery is recorded superior and to the left of the aorta (right hand side of the scan). Because the cross-sectional beam is oriented parallel to the short axis of the aorta this vessel has a normal circular configuration. In contrast the plane of the scan is oblique to the pulmonary artery causing it to have a half moon or sausage appearance. (From Feigenbaum H. *Echocardiography*, second edition. Lea & Febiger Philadelphia 1976)*

the contrasting pattern presented by the vessels when they exit the heart in a parallel fashion. In this configuration the scan which is parallel to the short

axis of one vessel will also be parallel to the short axis of the other. Thus the two vessels will both appear circular. In this example the aorta is superior to the pulmonary artery and both vessels have the expected circular appearance. This type of image is analogous to looking down the barrel of a double barrelled shot gun.

In patients with truncus arteriosus there is only one large vessel which appears as a single circle on the cross-sectional scan. These concepts suggest a relatively simple and straight forward method for differentiating anomalies of position and relative orientation of the great vessels.

The second problem which arises is the determination of ventricular situs. Sahn et al. noted that the configuration and motion pattern of the tricuspid valve is distinctly different than that of the two leaflet mitral valve (30).

#### TGV SAX



*Fig 10: Short axis cross-sectional echogram of the aorta and pulmonary artery from a patient with d-transposition of the great vessels. In this recording both the larger superior aorta and the smaller inferior pulmonary artery appear circular. This occurs because the great vessels are aligned parallel to each other and therefore when the plane of the scan is oriented parallel to the short axis of one vessel it must be parallel to the short axis of the other resulting in a similar appearance of both vessels. (From Feigenbaum, H. *Echocardiography*, second edition. Lea & Febiger Philadelphia 1976)*



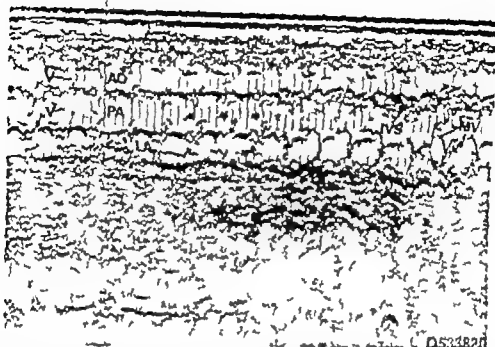


Fig 8 M-mode echocardiogram from a patient with d-transposition of the great vessels. The ultrasonic beam is scanned from the aorta and pulmonary artery on the left through the region of the mitral valve and into the left ventricle on the right. The aorta (AO) and pulmonary artery (PA) run parallel to each other with no evidence of an intervening crista supraventricularis. In addition echoes from both semi lunar valves are recorded simultaneously. The echoes from the interventricular septum (IVS) are continuous with those from the anterior wall of the pulmonary artery. The echoes from the mitral valve are continuous with the posterior wall of the pulmonary artery. This recording is typical of the M-mode features of transposition of the great vessels. (From Dillon et al. *Echocardiographic Manifestations of d-transposition of the Great Vessels*. *Amer J Cardiol* 32:74 1973)

Finally in patients with truncus arteriosus there is only a single large vessel. Using the cross-sectional system they then demonstrated that when the great vessels cross at their origin the plane of the cross sectional scan can be aligned parallel to the short axis of only one of the two arteries. As a result if the cross sectional scan is aligned parallel to the short axis of the aorta it must by definition be oblique to the short axis of the pulmonary artery. When presented in this fashion the aorta appears as a relatively circular structure while the pulmonary artery assumes a half moon or sausage shape. Fig 9 is an example of the normal short axis appearance of the great vessels at the level of the aortic and pulmonary valves. In this recording the aorta has a circular appearance while the pulmonary artery to which the scan is oblique appears to have a half moon or kidney shape. Fig 10 is a recording from a patient with transposition of the great vessels illustrating

## ACKNOWLEDGMENT

Supported in part by the Herman C. Krombert Fund and by Grants HL-06808 HL-05363 and HL-07188 from the National Heart Lung and Blood Institutes of the National Institutes of Health U.S. Public Health Service and the American Heart Association Indiana Affiliate

## REFERENCES

1. FEIGENBAUM H. Echocardiography Second Edition Lea & Febiger Philadelphia Pennsylvania 1976
2. GRAMIAK, R. and NAYDA M.C. Mitral Valve in Cardiac Ultrasound Gramiak and Naag editors St Louis The C.V. Mosby Co 1975
3. WEYMAN A.E. and FEIGENBAUM H. Echocardiography Where are we now are where are we going? (Editorial) Amer J Med 60 315 1976
4. FEIGENBAUM H.: Use of echocardiography in evaluating left ventricular function Second World Congress on Ultrasonics in Medicine Excerpta Medica June 1973
5. GRIFFITH J.M. and HERRY W.L. A sector scanner for real time Two-dimensional echocardiography Circulation 49 1147 1974
6. YOM ROMM D.T. THURSTONE F.L. Cardiac imaging using a phased array ultrasound system I System design Circulation 53 258 1976
7. EGGLETON R.C. FEIGENBAUM H. JOHNSTON K.W. WEYMAN A.E. DILLON J.C. and CHANG S. Visualization of cardiac dynamics with real time B-mode ultrasonic scanner Ultrasound in Medicine edited by Dennis White Plenum Press New York 1 385 1975
8. Edler I. Ultrasoundcardiogram in mitral valvular diseases Acta Chir Scandinavica 111 230 1956
9. Edler I. and Gustafson A. Ultrasonic cardiogram in mitral stenosis Acta Med Scandinavica 159 85 1957
10. COPE G.D. KISSLO J.A. JOHNSON M.L. and BEHAR V.S. A reassessment of the echocardiogram in mitral stenosis Circulation 52 664 1975
11. HERRY W.L. GRIFFITH J.M. MICHAELIS I.L. MCINTOSH C.L. MORROW A.W. and EPSTEIN S.E. Measurement of mitral orifice area in patients with mitral valve disease by real time two-dimensional echocardiography Circulation 51 827 1975
12. NICHOL P.M. GILBERT B.W. and KISSLO J.A. Two-dimensional echocardiographic assessment of mitral stenosis Circulation 55 120 1977
13. WANN L.S. WANN A.E. FEIGENBAUM H. DILLON J.C. JOHNSTON K.W. and EGGLETON, R.C. Comparison of mitral valve area determined by cross sectional echocardiography and by cardiac catheterization (in press)
14. WEYMAN A.E. FEIGENBAUM H. DILLON J.C. and CHANG S. Cross sectional echocardiography in assessing the severity of valvular aortic stenosis Circulation 52 828 1975

Since the tricuspid valve is normally associated with the anatomic right ventricle determination of the pattern of valvular motion permits an appreciation of the related ventricle and hence ventricular situs. These observations concerning great vessel and cardiac chamber orientation when combined with prior cross sectional observations concerning levels and types of left and right ventricular outflow obstruction suggest that the cross sectional echogram will become a valuable non-invasive tool for the diagnosis and assessment for various forms of complex congenital heart disease.

## DISCUSSION

In this report we have highlighted a number of the clinical areas in which cross sectional echocardiography has already proven to be of diagnostic value. These examples indicate that the increased field of vision provided by the cross sectional technique facilitates recording of individual cardiac structures and expands the area of the heart which is available for echocardiographic study while the dynamic spatially oriented display permits a unique appreciation of cross sectional cardiac anatomy and function. This combination of features expands enormously our ability to derive useful clinical data from the heart using pulsed reflected ultrasound.

Although at first glance one might feel that the quality of the information obtained from the cross sectional images is so far superior to that obtained by conventional M-mode recording that the M-mode technique will rapidly be replaced. While there are clearly clinical areas in which the cross sectional technique should surpass M-mode recording the high resolution rapid sampling rate and ease of data handling provided by the M-mode systems suggests that they will always find a place in the clinical examination. It is envisioned that in the future one will utilize the cross sectional system to obtain an overall view of cardiac structure and function. When detailed analysis of regional wall or valvular motion is required an M-mode recording of a selected portion of the scan will be obtained. The cross sectional scan therefore will permit a more intelligent selection of the specific regions to be examined while the M-mode recording will provide precise information in a readily useable format concerning the particular area selected. These combined features should provide the clinician with extremely useful and powerful tools for evaluating cardiac structure and function non invasively.

# IMPROVEMENT OF LATERAL RESOLUTION IN ULTRASONIC SYSTEMS

H. BOM, C. T. LANCÉE AND C. M. LIGTVOET

*From the section for Biomedical Technology Thoraxcenter Erasmus University Rotterdam The Netherlands*

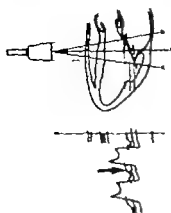
## INTRODUCTION

Resolution is the capability of echocardiographic systems to present separately closely lying structures. The resolution is usually defined in two directions: perpendicular to the sound beam (lateral resolution) and in the direction of the sound beam axis (axial resolution). If short ultrasonic pulses are used the axial resolution is in the order of one mm. For present medical practice this seems acceptable. In contrast the lateral resolution may constitute a major problem due to the finite beam width of ultrasonic devices. As a result echoes which originate from off axis structures may be displayed as if they were originating from structures on the beam axis. Both in time-motion (M-mode) registrations and two-dimensional imaging this distortion appears. Only the way of presentation is different. In an M-mode sectorscan the various cardiac structures are displayed as function of time and in a relation on the recording paper which is a function of the transducer aiming motion. In a two-dimensional image the correct geometrical structure orientation is presented. Thus if the beam shape in any two-dimensional imaging system and in single element M-mode registration were equal (which may be so with for instance a mechanical sectorscan) the errors which are introduced are the same.

A broad beamwidth will cause many spurious echoes (1). The beam width is a function of depth and depends on the transducer geometry and frequency. The most commonly used transducer in diagnostic techniques has the form of a disk which is arranged to transmit and receive energy at its surface. The sound beam is usually described as the near field and far field zone. For a given radius of the transducer the length of the near field zone increases with increasing frequency. In this near field zone the energy is mainly confined in a cylinder with a radius corresponding to the radius of the transducer disk (2). In the far field or Fraunhofer zone the energy is confined in a diverging central lobe and a number of secondary or side lobes. The energy in the side lobes is usually much smaller than in the main lobe. It should be realised that the beam pattern and the observed structures are three-dimensional; thus interpretation of errors within one plane seems an oversimplification of the situation. It should also be mentioned that the net

- 15 WEYMAN A E FEIGENBAUM H HURWITZ R A GIROD, D A and DILLON J C  
Cross sectional echocardiographic assessment of the severity of aortic  
stenosis in children *Circulation* 55 773 1977
- 16 WEYMAN A E DILLON J C FEIGENBAUM H and CHANG S Echocardio  
graphic patterns of pulmonic valve motion in valvular pulmonic stenosis  
*Amer J Cardiol* 36 644 1974
- 17 WEYMAN A E Pulmonary valve echo motion in clinical practice *Amer J  
Med* 62 843 855 1977
- 18 WEYMAN A E HURWITZ R A GIROD D A DILLON J C and FEIGENBAUM H  
Cross-sectional echocardiographic visualization of the stenotic pulmonary  
valve *Circulation* (in press)
- 19 DILLON J C HAINE C L CHANG S and FEIGENBAUM H Use of echocar-  
diography in patients with prolapsed mitral valve *Circulation* 43 503  
1971
- 20 KERBER R E Isaef S M and HANCOCK E W Echocardiographic patterns  
in patients with the syndrome of systolic click and late systolic murmur  
*New Engl J Med* 284 691 1971
- 21 DEMARIA A N KING J F BOGREN H G LIES J E and MASON D T  
The variable spectrum of echocardiographic manifestations of the mitral  
valve prolapse syndrome *Circulation* 50 33 1974
- 22 MARKIEWICZ W STONER J LONDON E HUNT S A and POPP R L Mitral  
valve prolapse in one hundred presumable healthy young females *Circu  
lation* 53 464 1976
- 23 SAHN D J ALLEN H D GOLDBERG S J and FRIEDMAN W F Mitral valve  
prolapse in children A problem defined by real time Cross sectional  
echocardiography *Circulation* 53 651 1976
- 24 GILBERT B W SCHATZ R A VON RAMM O T BEHAR V S and KISSLO J A  
Mitral valve prolapse Two-dimensional echocardiographic and angiographic  
correlation *Circulation* 54 716 1976
- 25 FEIGENBAUM H Echocardiographic examination of the left ventricle  
(Editorial) *Circulation* 51 1 1975
- 26 EDWARDS J E CAREY L S NEUFELD H N and LESTER R G  
Congenital heart disease vol I Philadelphia W B Saunders 1965 p 365
- 27 DILLON J C FEIGENBAUM H KONECKE L L KEUTEL J HURWITZ R A  
DAVIS R H and CHANG S Echocardiographic manifestations of d Trans  
position of the great vessels *Amer J Cardiol* 32 74 1973
- 28 FEIGENBAUM H Echocardiography Second Edition Lea & Febiger Phila  
delphia 1976 p 409
- 29 HENRY W L MARON B J GRIFFITH J M REDWOOD D R and EPSTEIN S E  
Differential diagnosis of anomalies of the great arteries by real time  
two dimensional echocardiography *Circulation* 51 283 1975
- 30 SAHN D J HENRY W L ALLEN H D GRIFFITH J M GOLDBERG S J  
The comparative utilities of real time cross sectional echocardiographic  
imaging systems for the diagnosis of complex congenital heart disease  
*Amer J Med* (in press)

Fig 1 Sagittal cardiac cross-section with transducer and beam directions  $b$  and  $a$  from which erroneous echoes may occur (see arrow)



In fig 2 a clinical example of this phenomenon is shown. As is found in similar situations in reality the mitral valve was normal although the multiple mitral valve echoes during systole could suggest mitral valve disease. Similarly echoes from the root of the aorta may sometimes contaminate the mitral valve registration and spurious echoes are very apparent when highly reflecting structures such as prosthetic valves are insonified.

#### ERRORS IN TWO-DIMENSIONAL IMAGING SYSTEMS

In fig 3 spurious echoes are schematically indicated for a linear array system and for a mechanical or phased sectorscan. In the multiscan or linear array situation in addition to the correctly presented point reflector  $P$  on

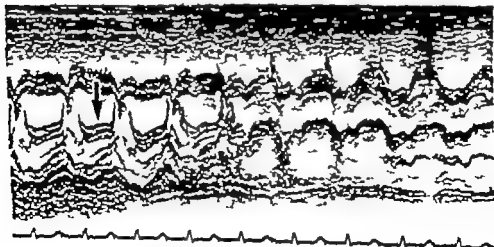


Fig 2: Clinical M-mode registration where multiple echoes are seen (arrow) possibly due to a situation as given in fig 1

effect of errors as they appear is also a function of parameters such as echo intensity gain settings : transducer sensitivity and recording paper or display parameters

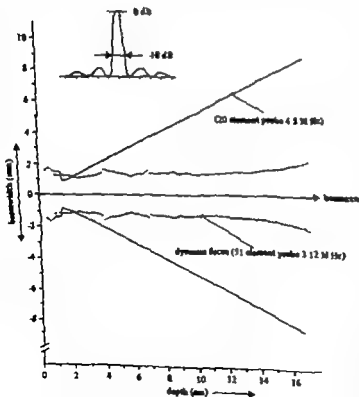
For a good lateral resolution a small beam width is required. As a first step towards a better lateral resolution transducers were constructed with an acoustic lens. This results in a fixed focal point. Another method which is often followed is the introduction of a curved transmission and reception surface whereby the wave front will cause a focussing effect at a fixed focal point. The focussing characteristics depend on frequency and aperture size. With constant aperture higher frequency results in better focussing. Ultrasonic attenuation increases with frequency thus the upper selectable frequency is limited. The transducer itself should remain relatively small for aiming purposes. This limits the aperture size. The main problem however is that with fixed focal point transducers only a better resolution in the vicinity of the focal point is obtained. In diagnostic ultrasound the target is a continuous object and an optimal solution calls for focussing over the entire field of view. This requires a dynamic focussing method.

In the following an indication is given of the errors that occur in single element and two dimensional imaging systems due to limited lateral resolution. Thereafter a solution will be described whereby a variable focussing is obtained electronically over the entire field of depth. It will be indicated how this can be implemented in single element as well as in a multi-element linear array system.

#### EXAMPLE OF M-MODE ERRORS

With an ideal pencil like ultrasonic beam the recorded echoes should represent the correct position of each reflecting structure on the beam axis. In fig 1 this situation is schematically shown for that part of the reflecting anterior mitral valve leaflet through which the ideal beam passes in direction a. Because of the imperfections in the beam width parts of the mitral valve in direction b and direction c are also creating an echo. Since the transducer transmits a short pulse and all echo systems are based on travel time measurements only the reflections from point 1 near the aorta and point 3 near the tip of the mitral leaflet are erroneously represented as dots in brightness modulation as indicated in fig 1. The arrow indicates the double or triple echoes which are often seen in systole in the anterior mitral leaflet registration.

The example shown at the top of Fig 4 shows no focussing at all with a flat wave front. At the bottom point focussing is obtained if a curved wavefront is constructed for acoustic waves in reception by delay of the incoming signals. This delay must be varied over the depth if a number of focus points are to result to cover the total depth. Since the beam pattern and the resulting lateral resolution is a function of the configuration in transmission and in reception some gain may be obtained by insertion of an axicon focus sing in transmission as also shown in Fig 4. The optimisation of the array was performed with a computer model. Calculation showed that for an effective focussing of 16 cm scan depth and with a given fundamental transducer a frequency of 3.12 MHz and aperture of 24 mm is needed. As an example a phased array transducer can be included in a linear array transducer and a so called linear phased array transducer is formed. In this situation a number of small elements will be used together as a subset of the entire linear array. Each focussing activity then will be repeated for an adjacent subset of elements. The subarray is divided into 12 elements of 2 mm width each. This results in a lateral spacing of 2 mm between two adjacent scans. For each application and frequency an optimal configuration can be calculated. For the linear array two-dimensional imaging transducer the principle was applied resulting in a new probe of 51 elements in total. In the earlier two-dimensional imaging system

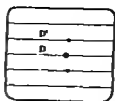


with the linear array principle we used 20 element-probes. In Fig 5 the beam width defined as the lateral position where the sound intensity has dropped to 10 dB as function of the depth is shown for the original 20 element system and for the 51 element dynamic focus.

Fig 5: Lateral beam resolution as measured at  $\sim 10$  dB as function of depth for the 20 element focussed linear array probe compared with the dynamically focussed 51 element probe.



## MULTISCAN



DISPLAY

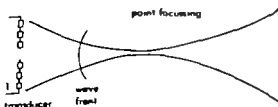
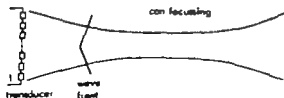
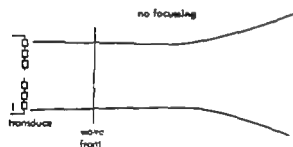
Fig 3 Image deformation diagrammatically constructed for a rectangularly and sectorially formed image (from *Echocardiology* N Bom editor published by Martinus Nijhoff the Hague 1977)

## SECTORSCAN



the display at distance  $D$  adjacent elements will see this reflector erroneously at distance  $D$ . The situation has been indicated for an arbitrary beam opening angle  $\alpha$ . On the display curved distortion will appear. A similar situation will occur with the sectorscan as shown at the bottom of fig 3. If the mechanically or electronically swept beam is pointing in direction 1 then reflector  $P$  is correctly represented on the display in beam direction 1. If however this beam is directed towards direction 2 then again  $P$  is seen and an echo presented on the display. Thus a slight curvature will result at a depth  $C$  much similar but in opposite direction to the one just described for the linear array system.

Illustration of various focussing methods shown for subgroup of element



## DYNAMIC FOCUSING (3)

If a transducer consists of a number of small elements it becomes possible to vary the pulse travel time between each individual element of the transducer and the focal point by means of electronic delay methods. With such a phased array transducer it is possible to maintain a good lateral resolution over the entire scan depth. In fig 4 the principle is explained schematically in the situation of linear array transducer. For each scan of the linear phased array a subset of elements is used as phased array.

Fig 4 Illustration of focussing possibilities with subset of elements. From top to bottom respectively no focussing action focussing as may be obtained in transmission and point focussing by introduction of a curved front in reception.

to frame or combinations in transmission and reception might be used to achieve optimal resolution

In this paper a system for dynamically focussing over the entire depth and over the complete two-dimensional image was described with focussing in the array plane only. Two prototypes are in operation and have been tested in various clinics. The improvement showed to be a step forward again and will certainly carry the applications beyond today's use where only direct observations of gross changes in dynamics and geometry of the heart in motion are studied.

#### REFERENCES

1. ROELANDT J, VAN DORP W G, BOM M, LAIRD J D and HUGENHOLTZ P G  
Resolution problems in echocardiology: a source of interpretation errors  
*Amer J of Cardiol* 37: 256-262, 1976
2. WELLS P M T. Physical principles of Ultrasonic Diagnosis. University of Bristol and United Bristol Hospitals. Bristol, England. Academic Press, London, 1969.
3. LIGTVOET C M, RIDDER, J, LANCEE C T, HAGEMETJER F and VLETTER W B  
A dynamically focused multiscan system. *Echocardiology* M. Bom editor, published by Martinus Nijhoff, The Hague, 1977.
4. ALAIS P, FIRK M and PERRIN J. Acoustic imaging with an electronically focussed and scanned array. *Ultrasonics in Medicine* 75-80, May 1975.



*Fig 6 Transducer for high resolution M-mode registrations. Transducer face (top) with individual circular symmetric elements. The complete transducer is shown as well (bottom)*



sing system. The gain in lateral resolution is particularly in deeper areas substantial. It may be concluded that with such parameters a reasonably good resolution can be maintained over the entire depth and thus over the entire 2 D image. Detailed information was further published by Ligtoet (see ref. 3).

The above described method is also applicable to single element M-mode technique. In that case for optimum lateral resolution here circular elements can be used. This does result in improvement of resolution in all directions perpendicular to the beam axis as well as over the entire depth. Again the optimum combination of the geometry, number of rings and frequency must be calculated. As an example a disk shaped transducer for M mode registrations is shown in Fig 6.

## DISCUSSION

With the introduction of the dynamic focus an entire new generation of equipment was introduced. Not only is the transducer of e.g. the two-dimensional imaging system much more complex with its 51 elements, also the electronic processing for transmission as well as reception is much more complicated. Future will tell if in practice the inherent complexity and thus increased costs of such improvements are indeed necessary for routine use.

It should be emphasized that here described focussing in two-dimensional images with a linear one dimensional array has been obtained as function of depth and in the plane of the array only. Lateral resolution will be improved if in future also focussing in the plane perpendicular to the array plane is introduced. As is suggested for instance focussing with a two-dimensional array and phase and antiphase steering of the elements to obtain three-dimensional focussing (4). In future such focussing may also be carried out with array configurations and signal processing equal or similar to the one described here but with additional acoustic element surfaces active and positioned in a plane perpendicular to the described array plane. Beam pattern variation from frame

to frame or combinations in transmission and reception might be used to achieve optimal resolution

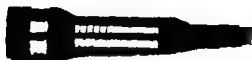
In this paper a system for dynamically focussing over the entire depth and over the complete two-dimensional image was described with focussing in the array plane only. Two prototypes are in operation and have been tested in various clinics. The improvement showed to be a step forward again and will certainly carry the applications beyond today's use where only direct observations of gross changes in dynamics and geometry of the heart in motion are studied.

#### REFERENCES

- 1 ROELANDT J, VAN DORP W G, BOM N, LAIRD J D and HUGENHOLTZ P G  
Resolution problems in echocardiology: a source of interpretation errors  
*Amer J of Cardiol* 37 256-262 1976
- 2 WELLS P M T. Physical principles of Ultrasonic Diagnosis. University of Bristol and United Bristol Hospitals. Bristol, England. Academic Press London 1969
- 3 LIGTYDET C.M, RIDDER J, LANCEE C T, HAGEMEIJER F and VLETTER W B  
A dynamically focused multiscan system. *Echocardiology* M. Bom editor published by Martinus Nijhoff the Hague 1977
- 4 ALAIS P, FINK M and PERRIN J. Acoustic imaging with an electronically focussed and scanned array. *Ultrasonics in Medicine* 75-80 May 1975



Fig 6 Transducer for high resolution M-mode registrations Transducer face (top) with individual circular symmetric elements The complete transducer is shown as well (bottom)



sing system The gain in lateral resolution is particularly in deeper areas substantial It may be concluded that with such parameters a reasonably good resolution can be maintained over the entire depth and thus over the entire 2 D image Detailed information was further published by Ligtoet (see ref 3)

The above described method is also applicable to single element M-mode technique be it that for optimum lateral resolution here circular elements can be used This does result in improvement of resolution in all directions perpendicular to the beam axis as well as over the entire depth Again the optimum combination of the geometry number of rings and frequency must be calculated As an example a disk shaped transducer for M-mode registrations is shown in Fig 6

## DISCUSSION

With the introduction of the dynamic focus an entire new generation of equipment was introduced Not only is the transducer of e g the two dimensional imaging system much more complex with its 51 elements also the electronic processing for transmission as well as reception is much more complicated Future will tell if in practice the inherent complexity and thus increased costs of such improvements are indeed necessary for routine use

It should be emphasized that here described focussing in two dimensional images with a linear one dimensional array has been obtained as function of depth and in the plane of the array only Lateral resolution will be improved if in future also focussing in the plane perpendicular to the array plane is introduced Also suggested for instance focussing with a two-dimensional array and phase and antiphase steering of the elements to obtain three-dimensional focusing (4) In future such focussing may also be carried out with array configurations and signal processing equal or similar to the one described here but with additional acoustic element surfaces active and positioned in a plane perpendicular to the described a ray plane Beam pattern variation from frame

to frame or combinations in transmission and reception might be used to achieve optimal resolution

In this paper a system for dynamically focussing over the entire depth and over the complete two-dimensional image was described with focussing in the array plane only. Two prototypes are in operation and have been tested in various clinics. The improvement showed to be a step forward again and will certainly carry the applications beyond today's use where only direct observations of gross changes in dynamics and geometry of the heart in motion are studied.

#### REFERENCES

1. ROELANDT J, VAN DORP W G, BOM M, LAIRD J D and HUGERHOLTZ P G  
Resolution problems in echocardiology: a source of interpretation errors  
*Amer J of Cardiol* 37 256-262 1976
2. WELLS P N T. Physical principles of Ultrasonic Diagnosis. University of Bristol and United Bristol Hospitals. Bristol, England. Academic Press London 1969
3. LIGTVOET C M, RIDDER J, LANCEE C T, HAGENHEIJER F and VLETTER W B  
A dynamically focused multiscan system. *Echocardiology* M. Bom editor published by Martinus Nijhoff the Hague 1977
4. ALAIS F, FINK M and PERRIN J. Acoustic imaging with an electronically focussed and scanned array. *Ultrasonics in Medicine* 75-80 May 1975



*Fig 6 Transducer for high resolution M-mode registrations Transducer face (top) with individual circular symmetric elements The complete transducer is shown as well (bottom)*



sing system The gain in lateral resolution is particularly in deeper areas substantial It may be concluded that with such parameters a reasonably good resolution can be maintained over the entire depth and thus over the entire 2 D image Detailed information was further published by Ligtoet (see ref 3)

The above described method is also applicable to single element M-mode technique be it that for optimum lateral resolution here circular elements can be used This does result in improvement of resolution in all directions perpendicular to the beam axis as well as over the entire depth Again the optimum combination of the geometry number of rings and frequency must be calculated As an example a disk shaped transducer for M-mode registrations is shown in Fig 6

## DISCUSSION

With the introduction of the dynamic focus an entire new generation of equipment was introduced Not only is the transducer of e g the two dimensional imaging system much more complex with its 51 elements also the electronic processing for transmission as well as reception is much more complicated Future will tell if in practice the inherent complexity and thus increased costs of such improvements are indeed necessary for routine use

It should be emphasized that here described focussing in two-dimensional images with a linear one-dimensional array has been obtained as function of depth and in the plane of the array only Lateral resolution will be improved if in future also focussing in the plane perpendicular to the array plane is introduced Alais suggested for instance focussing with a two-dimensional array and phase and antiphase steering of the elements to obtain three-dimensional focusing (4) In future such focussing may also be carried out with array configurations and signal processing equal or similar to the one described here but with additional acoustic element surfaces active and positioned in a plane perpendicular to the described a ray plane Beam pattern variation from frame



Fig 2

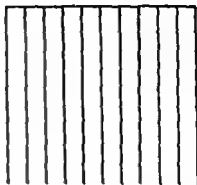


Fig 3

In mechanical sector scanners there is a single element transducer not unlike that used in standard ultrasound instrumentation. This single element transducer is moved rapidly through an arc which varies from 11 degrees to approximately 60 degrees. The electrical sector array approach utilizes a phased linear array in which the ultrasound beam is electronically steered at angles ranging from 0 to 90 degrees. This type of instrumentation is primarily used for cardiology applications in that the transducer's head size and resultant field of view is most suited for imaging thru the small intercostal spaces present in ultrasound cardiology examinations. However the sector array type of instrumentation is not optimally suited for abdominal imaging because of its pie-shaped field of view. There is also the disadvantage that with the sector array approach the area of the resultant beam having maximum line density directly corresponds to the area of minimum field of view. Conversely the area having the maximum field of view is also the area of minimum resolution due to the change in line spacing which increases as a function of depth (see fig 2).

The linear array system has a rectangular field of view and ranges in electronic complexity from totally unfocused to focused on both transmit and receive.

Because of its rectangular field of view the linear array system is ideally suited for abdominal imaging. However the physical size of the array makes it less effective in other applications. The limitations of field of view and loss in resolution with increased depth is overcome due to the uniform field of view (see fig 3).

We have elected to go with the linear array system as it is ideally suited for abdominal imaging and has potential in other areas of application such as breast, thyroid and cardiology.



# ULTRASOUND FLUOROSCOPY - WHAT IS IT AND OUR APPROACH TO YOUR REQUIREMENTS

J A MCLAIN

*From the Unirad Corporation Subsidiary of Ohio-Nuclear A Technicare Company Denver Colorado USA*

## ABSTRACT

A discussion on Ultrasound Fluoroscopy and how it relates to the traditional Real Time Instrumentation

This paper covers the various types of Ultrasound Fluoroscopy Instrumentation a few of the advantages and disadvantages of each and Unirad Corporation's approach to Ultrasound Fluoroscopy Also detailed discussions on the technical differences between their approach and the traditional Real Time Instrumentation itemizing electronic beam resolution control in some detail as to its advantages complexity and comparison to Real Time (Non-focused) and the traditional single element Ultrasound Instruments

---

Ultrasound Fluoroscopy is an imaging technique which in the past has also been referred to as real time imaging However even though Ultrasound Fluoroscopy and Real time imaging may appear to be the same there are major technical differences some of which will be covered in this paper The types of instrumentation available in Ultrasound Fluoroscopy fall into two separate categories

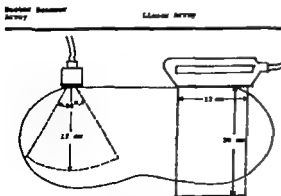


Fig 1 Field of view comparison.  
Abdominal scan

The differences in these two categories are the particular field of view chosen for display Fig 1 illustrates the difference with the sector array having a pie shaped field of view and the linear array a rectangular field of view

The field of view obtained through the use of a sector array can be achieved by either mechanical or electrical means

The features which we decided to include through considerable marketing studies of medical needs are listed in table I

A comparison of the tradition real time ultrasound system and our Ultrasound SonoFluoroscopy system is shown in table II reflecting the differences between these two types of instrumentation

Some of the major differences of particular interest and having a dramatic effect upon the instrument's resolution and diagnostic capabilities are TV format display as this permits an expanded grayscale display and smaller dot size an electronic beam resolution control which allows the operator through electronic focusing to optimize the beam's resolution at the depth of the tissue under study The variable grayscale dynamic range control allows the operator to optimize the instrument's grayscale processing for the particular patient organ or diagnosis required The multiple modes of operation give the instrument added flexibility for different types of ultrasound applications without the necessity of additional instrumentation

Our approach to satisfying the listed features was achieved with the SonoFluoroscope I

A closeup of the front panel and operator controls is shown in fig 4

The special importance of some of the specific features of the SonoFluoroscope I are explained in greater detail in the remainder of this paper

Fig 5 is a demonstration of the resolution capability of the instrument as it relates to line density

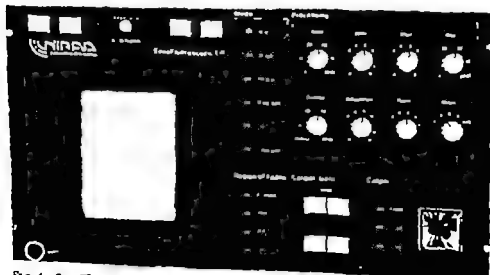


Fig. 4. SonoFluoroscope I

Table I

# SONOFLUOROSCOPE I FEATURES

- |   |   |
|---|---|
| 1 Television Format High Resolution Monitor                                     | 6 Electronic Beam Resolution Control (Electronic Beam Focusing) |
| 2 128 Line Resolution Display and Photography                                   | 7 Selectable Greatone Dynamic Range from 5 db to 40 db          |
| 3 Optional B-scan Interface for Post Data Processing                            | 8 Outline Processing  |
| 4 Ultrasound Fluoroscopy Image and A mode or complete TGC or ECG displayed      | 9 Wide Selection of Transducers Size and Frequency              |
| 5 Optional Time Motion Electronic Calipers Cardiac Gate and future developments | 10 Portable and Modular   |

Table II

## FEATURE COMPARISON RECTANGULAR FIELD OF VIEW UNIT

FEATURE	REAL TIME	SONOFLUOROSCOPE I
Display	X-Y Monitor - 120 Line Display (60 Lines of Information)	Television Monitor (360 Lines of Image Information)
Gain	Variable Gain Control	Calibrated Control 2 db steps 0 to 80 db
Time Gain Compensation	Far and Near Adjust No visual interpretation of settings	Standard 3 calibrated controls Initial Slope and Delay with visual interpretation on display
Resolution Control (Dynamic Focus)	None	Standard (Operator Adjustable)
Electronic Calipers	None	Option
Variable Transmit Power	None	Standard
Time Motion/ECG	None	Option
Frame Freeze	None	Standard
Dynamic Greatone Range	20 db	Variable 5 to 40 db
Video Outputs	Optional with T V Camera	Standard
B scan Interface	None	Option
T V Display	Optional with T V Camera	Standard

focal zone as a function of depth in each study. An example of this would be the variance between pediatric and adult cardiology. However, due to the physical size and cost of linear arrays it is not feasible to have a different transducer for each desired focal zone. This implies that it would be desirable to have electronic focusing which could be varied by the operator. But first let's look at some of the benefits of focusing and optimizing the arrays:

- |   |                                       |
|---|---------------------------------------|
| 1 Improved Resolution                                   | 5 Increase Angle of Off Axis Lobes    |
| 2 Increased Sensitivity Without Increasing Power Output | 6 Increase Dynamic Range              |
| 3 Increased Signal to Noise Ratio                       | 7 Instrument Adjustment Less Critical |
| 4 Decrease Off Axis Lobes                               |                                       |

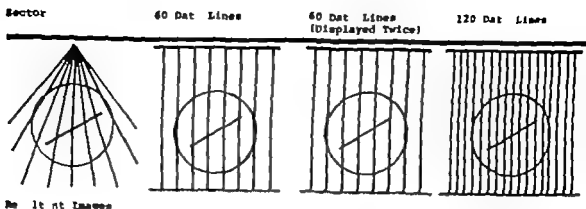
The SonoFluoroscope I includes a multiple focal zone transducer array which allows the operator to electronically adjust the focal zone without having to change the transducer.

The following 3 sketches reflect the dramatic improvement achieved through optimum transducer design and electronic focusing on both transmit and receive.

Fig 7 demonstrates the difference in off axis lobes and the main beam width. The improvement in decreasing the off axis lobe and decreased beam width is visualized by the operator in the dynamic range and lateral resolution capabilities of the instrument.

Fig 8 is a composite representation of the beam pattern of the main beam for different sensitivity ranges of 0 to 6 db, 6 db to 12 db and 12 db to 18 db. Through focusing each of these ranges has been decreased in width.

Fig 9 reflects the difference in the beam shapes due to focusing and variable focus. The shaded areas represent the portion of the beam where the lateral resolution is less than 5 mm. Since focusing is so important, why doesn't all the instrumentation include focusing on both transmit and receive? The answer is complexity as shown in the fig 10 which indicates the instrumentation degree of complexity required to achieving variable focusing on both transmit and receive as is done with the SonoFluoroscope I. With this type of instrumentation, an individual preamplifier, transmitter and receiver is required for each individual element of the array along with multiple delays to allow and compensate for the variable focal zones.



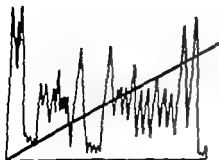
..

Fig 5 Line density/resolution

It is easy to see the loss in resolution as a function of depth with the sector array system due to the corresponding increase in line spacing. The difference in the diagnostic capability of a system including only half the number of data lines and the loss in resolution if the data lines are repeated twice with a simple offset for display is also shown.

Fig 6 is a theoretical representation of the different echo amplitudes received from the body during different examinations.

The total dynamic range required in order to display all the existing data is approximately 40 dB. However, the particular examination may only require a small range of these echo amplitudes. This indicates the need for a variable dynamic range control so the operator can optimize the instrument's dynamic range for the patient, organ, or particular diagnosis required. In addition to the variable dynamic range control, the SonoFluoroscope I includes an edge enhancement control which allows the operator to enhance the organ outlines or vascular structure to facilitate any particular diagnosis.



With the standard ultrasound systems employing the single element transducers, the operator usually changes the transducer for each patient to optimize the

Fig 6 Echo amplitude dynamic range

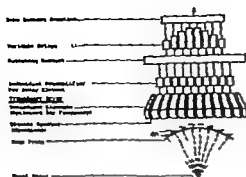


Fig 10: Focus (transcript and message)

Thus far only the improvements obtainable through electronic beam focusing has been discussed. Let's look at the difference between the single element transducer and any Phased Linear Array as shown in fig 11. The standard single element transducer has a symmetrical beam pattern while the linear array has two different dimensions of lateral resolution. Through electronic beam focusing the beam width in the X direction can be optimized to virtually the same as that obtainable with the focused single element transducers. However the Y dimension of the beam is directly related to the width of the transducer element which is optimized for the particular frequency of operation. Therefore even through the resolution of a linear array can be dramatically improved it still does not have equal lateral resolution when compared to the single element traditional instruments. With the difference in resolution capabilities it may be worthwhile also to compare some of the other advantages

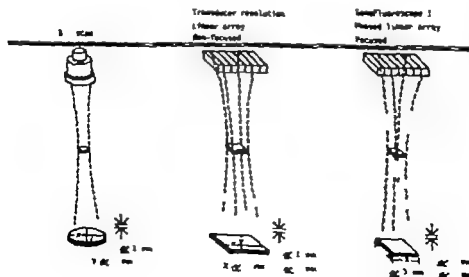
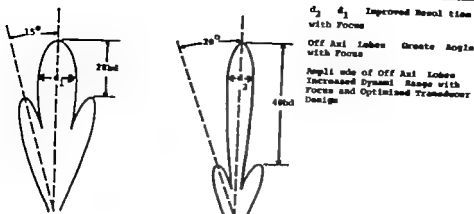


Fig 11

Non Focused

Focused

Fig 7 Off axis lobes

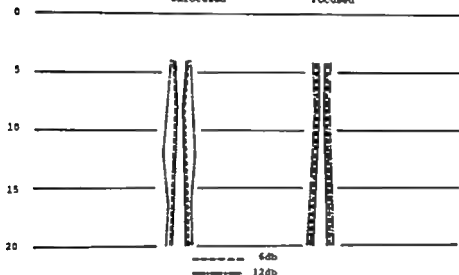


Depth

Unfocused

Focused

Fig 8 Beam pattern focused vs unfocused.



Depth

Non Focused

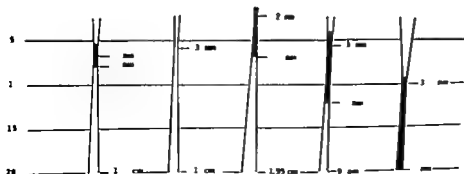
Graded Extended

Near

1d

Fm

Fig 9 Electronic beam resolution control for 2 x 5 kHz array



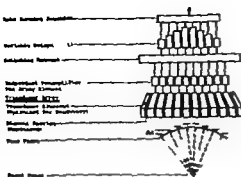
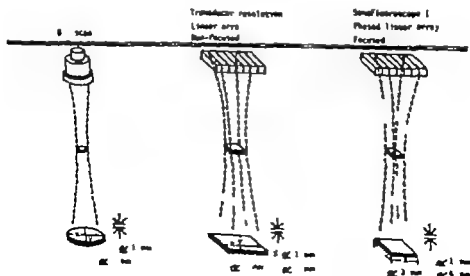


Fig 10 Focus (transmit and receive)

Thus far only the improvements obtainable through electronic beam focusing has been discussed. Let's look at the difference between the single element transducer and any Phased Linear Array as shown in fig 11. The standard single element transducer has a symmetrical beam pattern while the linear array has two different dimensions of lateral resolution. Through electronic beam focusing the beam width in the X direction can be optimized to virtually the same as that obtainable with the focused single element transducers. However the Y dimension of the beam is directly related to the width of the transducer element which is optimized for the particular frequency of operation. Therefore even though the resolution of a linear array can be dramatically improved it still does not have equal lateral resolution when compared to the single element traditional instruments. With the difference in resolution capabilities it may be worthwhile also to compare some of the other advantages



Flg 11



Non Focused

Focused

Fig 7 Off axis lobes

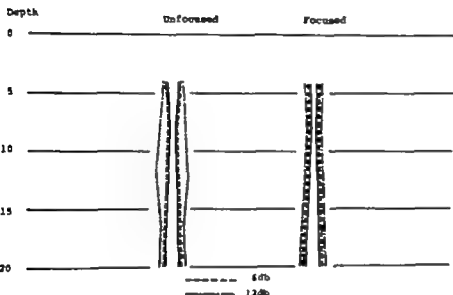
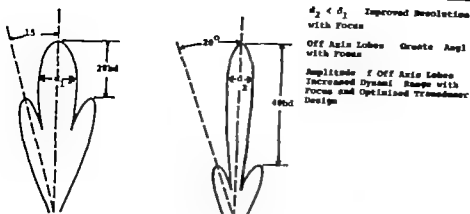


Fig 8 Beam pattern focused vs unfocused.

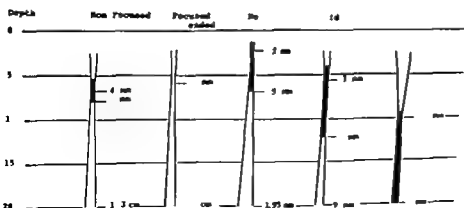


Fig 9 Electro-mechanical beam resolution control for 2x25 Mhz array

# PHASED ARRAY CARDIAC IMAGING: SYSTEM OPERATION RESULTS AND CLINICAL ROLE

J A KISSLO

*From the Department of Medicine Cardiovascular and Clinical Cardiology  
Laboratories Duke University Medical Center Durham North Carolina.*

## ABSTRACT

Proper clinical use of real-time two-dimensional echocardiography depends upon three major factors: the clinical questions posed of these imaging devices the interrelationship of this technique with other imaging techniques and the quality of the ultrasonic image. The Duke experience with this technique has been primarily based on results obtained with a focused phased array imaging system over the last three years. During this period of time we have observed that high-resolution cross-sectional ultrasonic images of cardiac structures provide unique diagnostic information that is not possible by any other method. Similarly this type of information allows the clinician to pose new questions concerning the use of diagnostic ultrasound in patient care. Improvements in image quality that have accompanied the addition of new scan formats and a broad-band transducer have enhanced the clinical reliability of diagnostic information.

---

Since the work of Edler and Hertz in 1954 (1) M-mode echocardiography has assumed a critical role in the clinical decision making process in patients with cardiovascular disease. With the recent advent of techniques for real time cross sectional imaging of cardiac structures the diagnostic capability of ultrasonic methods has been further enhanced.

One new imaging method employs phased array principles to electronically rather than mechanically sweep the ultrasound beam through a given cross sectional field of view. This report describes the basic clinical operating characteristics of these focused phased array imaging devices. In addition the general clinical role of real time two-dimensional echocardiography is discussed.

of the different types of ultrasound instrumentation. The distinct different advantages of the B Scanner and Ultrasound Fluoroscopy type of instrumentation are shown below.

#### B SCAN ADVANTAGES

- 1 High Resolution
- 2 Full cross section image
- 3 Tracks body contour
- 4 Multiple Greyscale  
(Processing (WDR NDR VDR))
- 5 Compound Scan
- 6 Post Data Processing
- 7 Anatomical Reference

#### ULTRASOUND FLUOROSCOPY ADVANTAGES

- 1 Rapid localization
- 2 Tracks moving structures
- 3 Portable
- 4 Decreased examination time
- 5 Less Technique involved
- 6 Synchronized Photography

The advantages of the standard Time/Motion Cardiology Instrument would be similar to those of the B-Scan device with the exception of storage and display capabilities. Both the standard B Scan or Cardiology Instrument and the Ultrasound Fluoroscopy Instrument have their place in the present ultrasound department with neither instrument being replaced by the other. Rather they complement each other to optimize the department's diagnostic capability and efficiency. We have carefully studied the ultrasound community's requirements for Ultrasound Fluoroscopy and feel that the SonoFluoroscope I will play a major role in the future of diagnostic ultrasound.

# PHASED ARRAY CARDIAC IMAGING SYSTEM OPERATION RESULTS AND CLINICAL ROLE

J A KISSLO

*From the Department of Medicine Cardiovascular and Clinical Cardiology  
Laboratories Duke University Medical Center Durham North Carolina*

## ABSTRACT

Proper clinical use of real-time two-dimensional echocardiography depends upon three major factors: the clinical questions posed of these imaging devices the interrelationship of this technique with other imaging techniques and the quality of the ultrasonic image. The Duke experience with this technique has been primarily based on results obtained with a focused phased array imaging system over the last three years. During this period of time we have observed that high-resolution cross sectional ultrasonic images of cardiac structures provide unique diagnostic information that is not possible by any other method. Similarly this type of information allows the clinician to pose new questions concerning the use of diagnostic ultrasound in patient care. Improvements in image quality that have accompanied the addition of new scan formats and a broad-band transducer have enhanced the clinical reliability of diagnostic information.

---

Since the work of Edler and Hertz in 1954 (1) M-mode echocardiography has assumed a critical role in the clinical decision making process in patients with cardiovascular disease. With the recent advent of techniques for real time cross sectional imaging of cardiac structures the diagnostic capability of ultrasonic methods has been further enhanced.

One new imaging method employs phased array principles to electronically rather than mechanically sweep the ultrasound beam through a given cross sectional field of view. This report describes the basic clinical operating characteristics of these focused phased array imaging devices. In addition the general clinical role of real time two-dimensional echocardiography is discussed.

## METHODS

### Patients

Ultrasonic images presented herein are from among the first 3 000 patients examined with this system. Patients underwent echocardiographic examination for a variety of clinical problems including rheumatic valvular, congenital, atherosclerotic and other forms of heart disease. During these phases of initial clinical trial, a variety of scan formats (e.g. varying sector arc width and line density), transducers, and display and recording devices were utilized and thus account for variations in image quality presented.

### Echocardiographic imaging system

Two dimensional echocardiograms were performed on all patients using a previously described (2,3) real-time phased array imaging system. The system uses a handheld 32 element transducer array that measures 14 x 24 mm at the site of skin contact and relies upon phased array principles to electronically steer and focus the sound beam through the structures under investigation. Real-time cross-sectional images of cardiac structures are presented in a circular sector format 50, 60 or 90 degrees in azimuth at a frame rate of 30 per second. A schematic diagram of the transducer and sector arc is shown in fig 1. Images are permanently recorded on videotape for later playback and analysis.

This prototype imaging system is undergoing continual modifications in an effort to improve system performance, image quality and clinical capability.

It is important to note that much detail is lost in the single frame scan images that constitute the illustrations in this paper. They were made from the videotape recordings by means of a 35 mm photograph of the sector arc

in the stop-frame mode. As such, there is a loss of visual integration of motion that normally accompanies real-time playback. Moreover, there is a severe degradation in image quality caused by photographing a single frame image from the videotape recording because of the fact that an individual vi-



Fig 1 Schematic diagram showing transducer and 90 degree scan plane

teotape frame represents the scan information collected in only 1/60th of a second. When operating in the 90 degree 160 line format therefore each single frame video field shows only one half (80 lines) of the information provided in the real time scan.

Additional images were obtained since December 1976 using a commercial prototype of this imaging system (Grumman Health Systems RT-400). This system is capable of producing cross sectional cardiac images in a 70 degree sector arc. Basic operating characteristics are similar to those previously described.

### Examination Technique

Ultrasound examinations were performed with the patients in the supine or left lateral positions. The transducer is placed over an aquasonic gel interface to the left of the sternal border between the second and fifth ribs and costal cartilages. An identical acoustic window to that used for time-motion examination of the heart is then utilized. Most favorable images of course are recorded when the transducer is held over an intercostal space rather than over the ribs, costal cartilages or sternum.

A standard echocardiographic examination is performed in a number of cross sectional planes through the heart (fig 2). Position I reveals images through the long axis of the left ventricle (aortic root, aortic valve, left atrium, mitral leaflets and the left ventricular cavity). Position II reveals portions of the right atrium, tricuspid leaflets and right ventricle in long axis. Serial cross sectional images through the short axis of the heart are then made. Position III is through the short axis

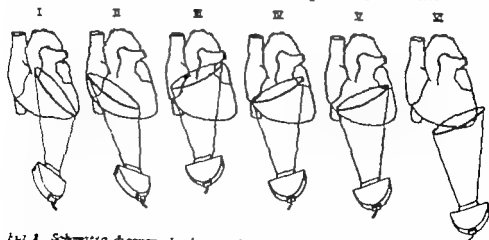


Fig 2. Schematic diagram showing six basic planes for two-dimensional echocardiography. See text for details. (Reproduced with permission, Circulation 1: 62 1978)

of the great vessels and atria usually at the level of the aortic valve. Position IV provides an image through the short axis of the left ventricle at the level of the mitral orifice. Position V provides a short axis view of the left ventricle at the level of the papillary muscles whereas position VI is a similar view at the level of the left ventricular apex.

As chest wall configuration and intrathoracic heart position are quite variable from patient to patient, a study is initially begun by locating the aortic root, mitral valve and portions of the left ventricle in long axis (position I). From that point, the remaining cardiac structures are then located by manipulating the transducer into the previously described position II-VI and other appropriate intermediate positions.

There is no current standard for the orientation of two-dimensional cardiac images. Earlier photographs presented in this manuscript will be oriented with the patient's chest wall to the left. More recent images will be oriented (as in M-mode echocardiography) with the chest wall at the top.

## RESULTS

This section describes several representative scans from patients undergoing examination with these prototype imaging systems. Fig 3 shows an early scan from the Duke system through the long axis of the aortic root and left ventricle (Position I). More recent scans through the long axis of the aortic root and mitral valve are seen in fig 4.

Normal mitral systolic coaptation is seen in Panel A and compared with two

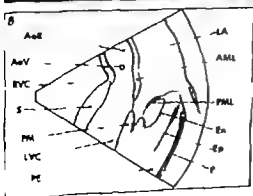


Fig 3 Panel A shows a photo from a stop action video tape frame through the long axis of the left ventricle (Position I). The aortic root is at the top of the scan and the left ventricular body toward the bottom. The chest wall is at the left. Note the pericardial effusion. AoR = aortic root, AoV = portion of aortic leaflets in diastole, RVC = right ventricular cavity, S = interventricular septum, PM = papillary muscles, LVC = left ventricular cavity, PE = pericardial effusion, LA = left atrium, AML = anterior mitral leaflet, PML = posterior mitral leaflet, En = endocardium, EP = epicardium and P = pericardium. (Reproduced with Circulation 53 282 1976)

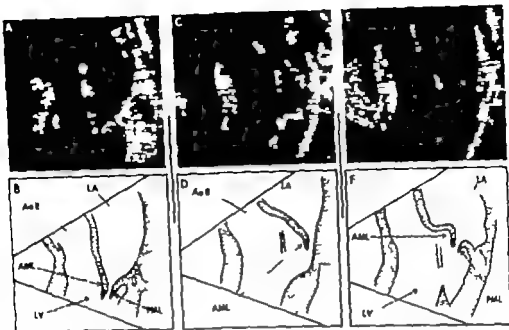


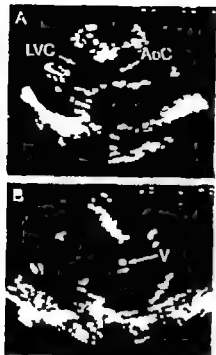
Fig 4 Systolic frames in the long axis of the mitral valve (Position I) The chest wall is at the left Panels A and B show a normal mitral valve Panels C and D show mitral prolapse with predominant anterior leaflet involvement Panels E and F show prolapse with more symmetrical involvement of anterior and posterior mitral leaflets AoR = aortic root LA = left atrium AVL = anterior mitral leaflet PML = posterior mitral leaflet LV = left ventricle



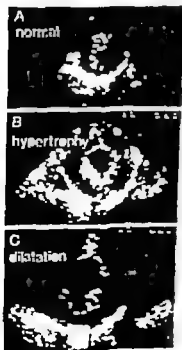
Fig 5 Long section of the left ventricle (Position I) The chest wall is to the left The ventricle is dilated.

variants of mitral prolapse in Panels C (anterior prolapse) and E (combined leaflet prolapse) The configuration of mitral prolapse pictured in Panel E is quite common in patients with atrial septal defect (4) Echocardiographic and angiographic comparisons of mitral prolapse would indicate that two-dimensional echocardiography is a much more sensitive method for detecting mitral prolapse than angiography or M-mode echocardiography (5)





*Fig 6 Two patients with similar long axis views of the left ventricle in isometric contraction. The chest wall is at the top. AoC = aortic cusps. LVC = left ventricular cavity. V = vegetation. Panel A shows the aortic cusps closed in pro-systole. Panel B shows a small vegetative mass.*



A markedly enlarged left ventricle is seen in long axis in fig 5. The 90 degree sector arc allows for visualization of most of the left ventricle despite its marked dilatation. Similar views of the long axis are shown in fig 6. The heart in Panel A is captured in isovolumic contraction with the aortic and mitral valves in the closed position. The photograph in Panel B shows a scan of a different patient at a similar time in the cardiac cycle. The bright target below the aortic valve was documented at surgery to be a bacterial vegetative mass. Real time two dimensional echocardiography has been shown to be a sensitive method for locating and sizing bacterial vegetative masses (6, 7).

Serial short axis scans through the left ventricle at the level of the papillary muscles (Position V) are seen in fig 7. A normal patient in Panel A is compared to one with severe left ventricular hypertrophy (Panel B) and one with marked ventricular dilatation (Panel C). The high resolution of the dynamically focused phased array system is seen in the details of endocardial trabeculations in all three patients.

Two-dimensional echocardiographic devices are useful for imaging pathologic problems hitherto impossible to detect by any other technique. The scan in fig 8 (Position V) is from a young girl with a severely dilated left ventricle. A large bacterial vegetative mass is seen on the endocardial surface of the inferior wall of the left ventricle. This mass

*Fig 7 Short axis views of the left ventricle (Position V) in three patients. The chest wall is at the top. Panel A is normal. Panel B shows ventricular hypertrophy and Panel C shows ventricular dilatation. Note the details of endocardial trabeculations seen in all three cases.*



Fig 8: Short axis (Position V) of a patient with large vegetative mass on the endocardial surface

was undetected by conventional M-mode echocardiography and angiography

Several studies have been conducted in this laboratory into the utility of real time two-dimensional echocardiography for the detection of abnormal left ventricular geometry. One such detailed study showed this method to compare quite favorably to angiography for the detection of ventricular asynergy. Fig 9 shows a left ventricular short axis (Position V) of a patient with severe pulmonary hypertension (Panel A) that resulted in compression of the left ventricle. The companion angiographic views reveal a dilated, poorly contractile

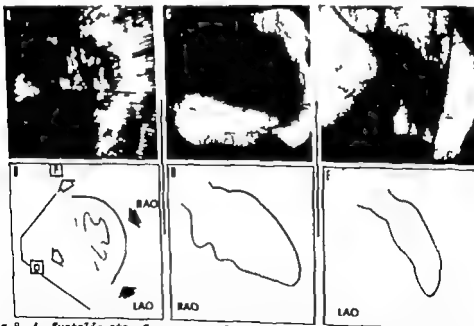
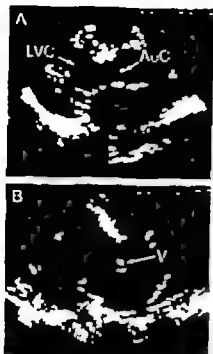
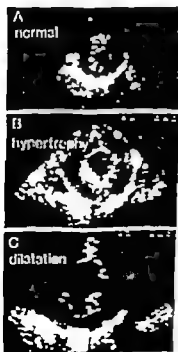


Fig 9 A: Systolic stop-frame image through the short axis (Position V) of the left ventricle in a patient with pulmonary hypertension. The chest wall is at the left. The ventricle is somewhat flattened in comparison to the normal seen in fig 4 C. B: Schematic diagram of the scan image showing the orientation of the radiographic planes of view. Because the ventricle is flattened, it appears lightly dilated and poorly contractile in the RAO angiographic projection (C and D) while it is narrow and well contractile in the LAO projection (E and F). Both angiographic frames are in systole. (Reproduced with permission: Circulation 53:134, 1977)



*Fig 6 Two patients with similar long axis views of the left ventricle in isometric contraction. The chest wall is at the top. AoC = aortic cusps. LVC = left ventricular cavity. V = vegetation. Panel A shows the aortic cusps closed in pre-systole. Panel B shows a small vegetative mass.*



A markedly enlarged left ventricle is seen in long axis in fig 5. The 90 degree sector arc allows for visualization of most of the left ventricle despite its marked dilatation. Similar views of the long axis are shown in fig 6. The heart in Panel A is captured in isovolumic contraction with the aortic and mitral valves in the closed position. The photograph in Panel B shows a scan of a different patient at a similar time in the cardiac cycle. The bright target below the aortic valve was documented at surgery to be a bacterial vegetative mass. Real time two-dimensional echocardiography has been shown to be a sensitive method for locating and sizing bacterial vegetative masses (6, 7).

Serial short axis scans through the left ventricle at the level of the papillary muscles (Position V) are seen in fig 7. A normal patient in Panel A is compared to one with severe left ventricular hypertrophy (Panel B) and one with marked ventricular dilatation (Panel C). The high resolution of the dynamically focused phased array system is seen in the details of endocardial trabeculations in all three patients.

Two-dimensional echocardiographic devices are useful for imaging pathologic problems hitherto impossible to detect by any other technique. The scan in fig 8 (Position V) is from a young girl with a severely dilated left ventricle. A large bacterial vegetative mass is seen on the endocardial surface of the inferior wall of the left ventricle. This mass

*Fig 7 Short axis views of the left ventricle (Position V) in three patients. The chest wall is at the top. Panel A is normal. Panel B shows ventricular hypertrophy and Panel C shows ventricular dilatation. Note the details of endocardial trabeculations seen in all three cases.*

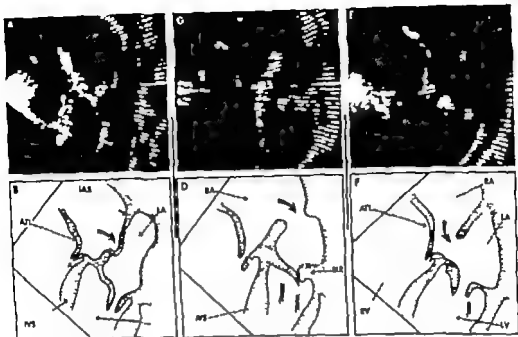


Fig 11 Systolic frames in the long axis of the tricuspid valve and interatrial septum (Position II). The chest wall is at the left. Panels A and B are from a normal subject. Arrow in B indicates the area of the foramen ovale. Panels C and D are from a patient with an ostium secundum atrial septal defect. Arrow in D indicates the area of the septal defect. Panels E and F are from a patient with an ostium primum atrial septal defect. Arrow in F indicates the area of the septal defect. ATL - anterior tricuspid leaflet; IAS - interatrial septum; IVS - interventricular septum; RA - right atrium; RV - right ventricle; LV - left ventricle; other abbreviations as in fig 4.

(Position II) in a normal patient (Panel A), a patient with a secundum atrial septal defect (Panel C) and a patient with an ostium primum atrial septal defect (Panel E). Although the sensitivity of these imaging systems for detecting patients with atrial septal defect is as yet unknown (4), these photos prompt hope in this possibility.

## DISCUSSION

Since first clinically used in 1954 (1), time motion echocardiography has justifiably enjoyed wide clinical application in the diagnosis of a variety of cardiac disorders. It cannot be assumed, however, that a one-dimensional echo image of a moving heart is a completely fair representation of the details of cardiac anatomy or motion. Indeed, there are two basic reasons to believe otherwise. First, angiographic studies into the complexities of left ventricular contraction clearly indicate that the left ventricle undergoes sequential contraction manifest by a series of rotational and other three

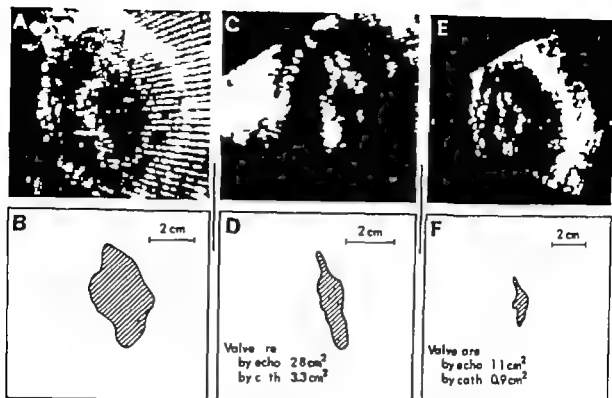


Fig 10 Panel A shows a diastolic frame through the short axis of the left ventricle in a normal individual (Position IV). The chest wall is at the left. Note the round contour of the left ventricular wall and the tips of the mitral valve leaflets (anterior on the left posterior on the right) within the left ventricular chamber. Panel B schematically shows the area between the leaflets. Because this area does not represent the mitral valve orifice normally it was not planimeted. Panel C shows a short axis diastolic frame in a patient with mild mitral stenosis. Note the thickening and irregularity of the mitral leaflets and the fusion of the commissures. Panel D schematically shows the mitral valve orifice area of this patient. Panels E and F are comparable to panels C and D for a patient with severe mitral stenosis. Note the irregular slit-like orifice.

ting ventricle in the RAO view (Panel C) and a narrow vigorously contracting ventricle in the orthogonal LAO view (Panel E). Thus, distortion of the ventricle as determined by echocardiography due to pulmonary hypertension may result in an erroneous impression of poor ventricular performance if only single plane RAO angiography is used at catheterization.

This method of imaging is also useful for evaluating the severity of mitral stenosis (9). Short axis scans through the level of the mitral orifice (Position IV) are seen in fig 10. Panel A shows a normal orifice while Panels C and E show progressive degrees of mitral stenosis.

Because of the wide sector arc and spatial relationships of ultrasonic targets, these systems are suitable for the evaluation of substernal targets such as tricuspid valve and interatrial septum. Fig 2 shows scans through the long axis of the right ventricle, tricuspid valve and interatrial septum.

Second the use of other diagnostic techniques such as cineangiography or radioisotope methods will aid in defining the clinical role of each method. The geometric configuration of the short axis of the left ventricle seen by echocardiography in fig 9 was a significant aid in interpreting the cine-angiographic information.

Third continuing development and use of two-dimensional echocardiography has shown progressive advances in image quality parameters such as resolution and gray scale. As imaging systems have evolved more accurate target information has become available. It is reasonable to believe that as this process continues new and reliable applications of cross sectional echocardiographic information will become available.

#### ACKNOWLEDGEMENT

Supported in part by USPHS Grants HL-12716 HL-14828 HL-17670 and ES-01613

#### REFERENCES

1. EDLER I, HERTZ C H. The use of ultrasonic reflectoscope for the continuous recording of movements of heart walls. *Kungl Fysiograf Sällskap Lund Förh* 24 1 1954
2. VON RAMM O T, THURSTONE F L. Cardiac imaging using a phased array ultrasound system I. System design. *Circulation* 53 258 1976
3. KISSLO J, VON RAMM O T, THURSTONE F L. Cardiac imaging using a phased array ultrasound system II. Clinical technique and application. *Circulation* 53 262 1976
4. LIEPPE W, SCALLION R, BEHAR V S, KISSLO J A. Two-dimensional echocardiographic findings in atrial septal defect. *Circulation* (in press)
5. GILBERT B W, SCHATZ R A, VON RAMM O T, BEHAR V S, KISSLO J A. Mitral valve prolapse. Two-dimensional echocardiographic and angiographic correlation. *Circulation* 54 716 1976
6. GILBERT B W, HANEY R S, CRAWFORD F, McLELLAN J, GALLIS H A, JOHNSON M L, KISSLO J A. Vegetative endocarditis. Two-dimensional echocardiographic assessment of vegetative endocarditis. *Circulation* 55 346 1977
7. KISSLO J, VON RAMM O T, HANEY R, JONES R, JUK S S, BEHAR V S. Echocardiographic evaluation of tricuspid valve endocarditis. An M-mode and two-dimensional study. *Amer J of Cardiol* 38 502 1976
8. KISSLO J A, ROBERTSON D, GILBERT B W, VON RAMM O T, BEHAR V S. A comparison of real time two-dimensional echocardiography and angiography in detecting left ventricular asynergy. *Circulation* 55 134 1977
9. NICHOL P M, GILBERT B W, KISSLO J A. Two-dimensional echocardiographic assessment of mitral stenosis. *Circulation* 55 120 1977

dimensional movements. It is difficult to imagine that data derived from a one dimensional echo recording faithfully reflects these complexities of motion. Second, while it is possible to obtain useful information concerning intracardiac spatial relationships by sweeping the ultrasound transducer from structure to structure from a relatively fixed position on the chest wall, it cannot be assumed that these time-motion recordings represent a true picture of the spatial relationships between the targets. The resulting images are, of course, distorted by both the time it takes to perform the sweep and the changing transducer to target distance.

Real-time two-dimensional echocardiography extends the use of M-mode for evaluation of the heart by providing spatial relationships to cardiac ultrasonic target information. The specific advantages of the focused phased array approach are the wide field of view, relatively small and easily manipulable transducer, high resolution and computer controlled scan format. The latter capability provides for easy interchange of transducers and scan format in order to maximize image quality. These systems are unfortunately not presently suited for examination of neonates or small infants. Narrow near field aperture, impaired resolution within the proximal 3 cm and transducer ring down artifact all contribute to this problem.

In just over three years of clinical use at the Duke University Medical Center, in excess of 3,000 patients have been examined for a variety of congenital and valvular or other acquired cardiac problems. Although the present clinical demand for two-dimensional echocardiographic examinations exceeds M-mode by 25%, it is proper to think of the two techniques as complimentary. The M-mode records one-dimensional sonic information in time. Certain observations, such as the rapid oscillations of the mitral valve in aortic insufficiency or timing of valvular or heart wall movements with the cardiac cycle, are much easier made by M-mode. On the other hand, the spatial characteristics provided by two dimensional echocardiography give a unique view of cardiac anatomy and provide clinical information that is difficult or impossible to obtain by other methods.

To define the clinical role of two-dimensional echocardiography, one must examine three basic points. First, recognizing the advantages and limitations of this tool, the echocardiographer must seek unique diagnostic applications of the technique. Appreciation of the ventricular endocardial mass in fig 8 is one such application.

Second the use of other diagnostic techniques such as cineangiography or radioisotope methods will aid in defining the clinical role of each method. The geometric configuration of the short axis of the left ventricle seen by echocardiography in fig 9 was a significant aid in interpreting the cine angiographic information.

Third continuing development and use of two-dimensional echocardiography has shown progressive advances in image quality parameters such as resolution and gray scale. As imaging systems have evolved more accurate target information has become available. It is reasonable to believe that as this process continues new and reliable applications of cross sectional echocardiographic information will become available.

#### ACKNOWLEDGEMENT

supported in part by USPHS Grants HL-18716 HL-14828 HL-17670 and HS-01813

#### REFERENCES

1. EDLER I, HERTZ C H. The use of ultrasonic reflectoscope for the continuous recording of movements of heart walls. Kungl Fysiograf Sällskap Lund Förh 24 1 1954
2. VON RAMM O T, THURSTONE F L. Cardiac imaging using a phased array ultrasound system I. System design. Circulation 53 258 1976
3. KISSLO J, VON RAMM O T, THURSTONE F L. Cardiac imaging using a phased array ultrasound system II. Clinical technique and application. Circulation 53 262 1976
4. LIEPPE W, SCALLION R, BEHAR V S, KISSLO J A. Two-dimensional echocardiographic findings in atrial septal defect. Circulation (in press)
5. GILBERT B W, SCHATZ R A, VON RAMM O T, BEHAR V S, KISSLO J A. Mitral valve prolapse. Two-dimensional echocardiographic and angiographic correlation. Circulation 54 716 1976
6. GILBERT B W, HANEY R S, CRAWFORD F, MCLELLAN J, GALLIS H A, JOHNSON H L, KISSLO J A. Vegetative endocarditis. Two-dimensional echocardiographic assessment of vegetative endocarditis. Circulation 55 346 1977
7. KISSLO J, VON RAMM O T, HANEY R, JONES R, JUK S S., BEHAR V S. Echocardiographic evaluation of tricuspid valve endocarditis. An M-mode and two-dimensional study. Amer J of Cardiol 38 502 1976
8. KISSLO J A, ROBERTSON D, GILBERT B W, VON RAMM O T, BEHAR V S. A comparison of real time two-dimensional echocardiography and angiography in detecting left ventricular asymmetry. Circulation 55 134 1977
9. NICHOL P H, GILBERT B W, KISSLO J A. Two-dimensional echocardiographic assessment of mitral stenosis. Circulation 55 120 1977



## THE CLINICAL UTILITY OF TWO-DIMENSIONAL ECHOCARDIOGRAPHY

H RAKOWSKI \* R P MARTIN J W FRENCH AND R L POPP

*From the Division of Cardiology and Pediatrics Cardiology Stanford University School of Medicine Stanford California*

When in 1954 Edler and Hertz first described the use of high frequency ultrasound to record cardiac motion (1) even the most optimistic observer would have found it difficult to predict the consequences of this innovation. Initial applications of the technique included the non invasive diagnosis of mitral stenosis (2) pericardial effusion (3) and atrial myxomas (4). As the clinical usefulness of M-mode echocardiography has grown it has played an ever increasing role in the assessment of cardiac disease (5,6).

The development of two-dimensional echocardiography represents a major step in the evolution of ultrasound as a diagnostic tool. The greatest advantage of two-dimensional echocardiography is that it permits the correct identification of the spatial orientation of cardiac structures throughout the cardiac cycle. This is due to the ability to image the heart in long axis and multiple short axis planes with a wide field of view. The information provided is similar to that obtained at cardiac angiography with the advantage of clearly visualizing valvular structure and motion.

At the Stanford University Medical Center for the past 18 months we have used a prototype and more recently a production model of the Varian V 3000 phased array ultrasonic sector scanner. This system utilizes a hand held 32 element transducer which is focused at 7 cm by an acoustic lens. The echo beam is electronically steered through an 80 degree sector arc with a maximum recordable tissue depth of 21 cm. An M-mode printout can be obtained from any sector line using a movable cursor. The method of obtaining studies using a wide-angle phased array system has previously been described (7). Since the same physical properties of ultrasound apply to both M-mode and two-dimensional echocardiography patients with thin chests and without chest wall deformity yield high quality studies using either technique.

---

\* Present address Non Invasive Laboratory Toronto General Hospital  
101 College Street West Toronto Canada

In patients such as those with obstructive lung disease in whom it is difficult to obtain a standard study additional acoustic windows such as the cardiac apex and subxyphoid area can be used more effectively since the orientation of the echo beam is known. With two-dimensional echocardiography useful studies therefore can be obtained in almost all patients.

Studies are recorded on videotape for playback and analysis. The optimal method of analyzing abnormalities of temporal motion of cardiac structures is at real time or slow motion speed. The quantification of parameters such as left ventricular volumes, ejection phase indices and valve areas is made using stop-action single fields of a two field/frame video image. The illustrations used in this article were taken from stop-action video fields using a Polaroid camera. Since with this method all of the information present in one video frame is not being displayed there is some degradation of picture quality. In addition it is difficult to adequately display abnormalities that primarily involve the motion of cardiac structures.

We will now briefly focus on the initial clinical applications of two-dimensional echocardiography. Besides providing unique information about cardiac structure and function it has been particularly valuable in explaining many of the patterns seen on M-mode echocardiography.

#### ISCHEMIC HEART DISEASE

The ability of wide-angle two-dimensional sector scanning to assess left ventricular dysfunction is more fully described in an accompanying paper. Segmental wall motion abnormalities can readily be detected by real time analysis of both long and short axis sector scans (8). The site and extent of left ventricular aneurysms can be determined in a manner similar to angiography (9, 10). In addition to the qualitative assessment of wall motion abnormalities currently semiquantitative measurements of left ventricular volumes and ejection phase indices can be made regardless of the presence of left ventricular asynergy. A potentially important role of two-dimensional echocardiography is the serial non-invasive determination of left ventricular function following medical interventions such as afterload reduction or surgical interventions such as coronary artery bypass grafting. While the left main coronary artery can often be visualized by two-dimensional echocardiography (11) in our experience the presence of significant proximal stenosis cannot reliably be predicted.

## THE CLINICAL UTILITY OF TWO-DIMENSIONAL ECHOCARDIOGRAPHY

H RAKOWSKI \* R P MARTIN J W FRENCH AND R L POPP

*From the Division of Cardiology and Pediatric Cardiology Stanford University School of Medicine Stanford California*

When in 1954 Edler and Hertz first described the use of high frequency ultrasound to record cardiac motion (1) even the most optimistic observer would have found it difficult to predict the consequences of this innovation. Initial applications of the technique included the non-invasive diagnosis of mitral stenosis (2) pericardial effusion (3) and atrial myxomas (4). As the clinical usefulness of M-mode echocardiography has grown it has played an ever increasing role in the assessment of cardiac disease (5, 6).

The development of two-dimensional echocardiography represents a major step in the evolution of ultrasound as a diagnostic tool. The greatest advantage of two dimensional echocardiography is that it permits the correct identification of the spatial orientation of cardiac structures throughout the cardiac cycle. This is due to the ability to image the heart in long axis and multiple short axis planes with a wide field of view. The information provided is similar to that obtained at cardiac angiography with the advantage of clearly visualizing valvular structure and motion.

At the Stanford University Medical Center for the past 18 months we have used a prototype and more recently a production model of the Varian V 3000 phased array ultrasonic sector scanner. This system utilizes a hand held 32 element transducer which is focused at 7 cm by an acoustic lens. The echo beam is electronically steered through an 80 degree sector arc with a maximum recordable tissue depth of 21 cm. An M-mode printout can be obtained from any sector line using a movable cursor. The method of obtaining studies using a wide-angle phased array system has previously been described (7). Since the same physical properties of ultrasound apply to both M-mode and two dimensional echocardiography patients with thin chests and without chest wall deformity yield high quality studies using either technique.

---

\* Present address: Non Invasive Laboratory Toronto General Hospital  
101 College Street West Toronto Canada

and short axis planes respectively. The systolic anterior motion present on M-mode studies appears to be due to systolic anterior motion of the lower one-third of the mitral valve and/or chordae tendineae. Following septal myectomy the area of muscle removed can be seen as a defect in the septum and the effect of surgery on the degree of systolic anterior motion and the dimension of the left ventricular outflow tract can readily be determined.

In patients with restrictive cardiomyopathy due to cardiac amyloidosis the findings are similar to those seen on M-mode studies (13). The left ventricle is symmetrically thickened with normal or decreased volume and the septum is akinetetic with little or no systolic thickening. Pericardial effusion and/or thickening may also be present.

#### PERICARDIAL EFFUSION

Echocardiography is the simplest and most sensitive means of detecting the presence of pericardial effusion (3). Two-dimensional echo studies in patients with pericardial effusion (fig 2) have demonstrated several points (14). Most effusions first start as collections of fluid in the pericardial space at the level of the mitral annulus. This explains why M-mode studies in patients with minimal effusions sometimes reveal an echo-free space at the level of the mitral valve but not at the level of the left ventricular study. As the effusion enlarges its distribution may not always be symmetrical and there may be pooling of fluid medially or laterally. With sitting or standing the distribution of the fluid is more apical. Loculated effusions can more readily be recognized by two-dimensional echocardiography than by M-mode. We are currently studying the usefulness of two-dimensional echocardiography during pericardiocentesis to visualize the exploring needle.

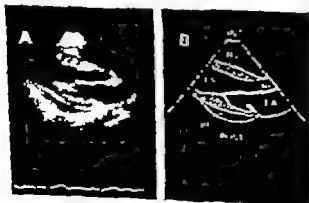


Fig 2: Panel A is a top-down frame taken in the long axis plane with panel B the accompanying line diagram. A moderate size posterior pericardial effusion is seen. PE - pericardial effusion other abbreviations as in fig 1.

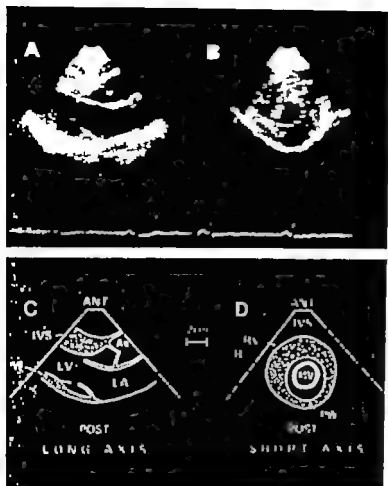


Fig 1 Panels A and B are diastolic stop-action frames taken in the long axis and mitral short axis planes from a patient with idiopathic hypertrophic subaortic stenosis (IHSS). Panels C and D are corresponding line diagrams. The degree and extent of asymmetric septal hypertrophy is assessed from analysis of both views. ANT = anterior POST = posterior R = right L = left IVS = interventricular septum PW = posterior left ventricular wall LV = left ventricle RV = right ventricle Ao = aorta LA = left atrium MV = mitral valve.

## CARDIOMYOPATHIES

In patients with congestive cardiomyopathy a dilated heart with global hypokinesis is generally seen. The closed mitral valve leaflets assume a more vertical orientation due to ventricular dilatation. The increased leaflet reflectance and the systolic layering of mitral echoes often seen on M-mode examination appears to be due to inadequate lateral resolution of the echo beam with different parts of the leaflets recorded in the same apparent plane. In severe cases all cardiac chambers are enlarged, there is little left atrial emptying and the ejection fraction is low.

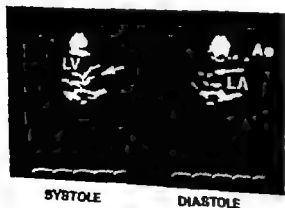
In patients with idiopathic hypertrophic subaortic stenosis (see fig 1) Martin et al (12) have shown the usefulness of two dimensional echocardiography. Interventricular septal thickness can more reliably be defined with better localization of the right side of the septum than with M-mode methods. Septal thickness may vary from the level of the mitral valve to the level of the standard M-mode left ventricular study and care must be taken to standardize the site of measurement. Besides defining increased septal thickness the length and width of the abnormality can be determined from long

separation seen by two-dimensional echocardiography is a semiquantitative estimate of the severity of the stenosis(19) As well stenosis due to valve doming can be detected whereas it is usually missed on M-mode studies (19) Two-dimensional echocardiography may also be more sensitive and specific than M-mode echocardiography in the detection of valvular pulmonary stenosis (20)

The presence of valvular regurgitation is suggested by the same criteria used on M-mode examination (5 6) Two-dimensional echocardiography is particularly useful in determining the cause of non rheumatic mitral regurgitation In patients with mitral valve prolapse two major abnormalities contribute to the prolapsing of the mitral leaflets posterior to the level of the AV groove These are 1) mitral leaflet redundancy with systolic superior arching into the left atrium (21 22) and/or 2) abnormalities of posterobasal left ventricular and mitral annular motion resulting in apparent loss of systolic support for the mitral leaflets (22) The systolic anterior motion of the anterior mitral leaflet sometimes seen in this condition appears to be due to systolic anterior motion of chordae tendineae Ruptured chordae tendineae flail leaflets and mitral annular calcification or thickening can also be detected sometimes with better reliability than on M-mode studies

#### INTRACARDIAC MASS LESIONS

Two-dimensional echocardiography can be used as an alternative or adjunct to cardiac angiography in selected patients with intracardiac masses (23) When an intracardiac mass is seen differentiation between lesions such as cardiac tumors clots or vegetations often cannot be made and the echo findings must be correlated with the clinical setting This technique is supe-



*Fig 4: The left and right panels are stop-action frames taken in systole and diastole respectively. A large mobile mitral valve mass secondary to infective endocarditis is seen (large arrow left panel). Abbreviations as in fig 1*



Fig 3 Panels A and B are stop-action frames taken in the long axis plane in systole and diastole respectively in a patient with mitral stenosis. Note the very dilated left atrium. The anterior (upper white arrows) and posterior mitral leaflets (lower white arrows) are thickened. The anterior leaflet is tethered at its distal end but is relatively mobile at its mid portion as shown by its anterior diastolic doming (upper white arrow panel B). Panel C was taken in the short axis plane at the level of tip of the mitral valve. Again the thickening of both leaflets can be appreciated. The mitral orifice is well visualized (white arrow panel C) and is small and irregular. Abbreviations as in fig 1.

and to monitor the withdrawal of the pericardial fluid

### VALVULAR HEART DISEASE

One of the most promising early applications of two dimensional echocardiography has been the assessment of mitral stenosis (15-17). Recent studies have shown that the mitral diastolic EF slope does not correlate well with mitral valve areas determined by the Gorlin formula (16). Two-dimensional echocardiography provides a more direct measurement of mitral valve area in that the mitral valve orifice can directly be recorded in the short axis plane (fig 3). A number of authors using this technique have reported good correlations with the Gorlin formula (15-17) and in some patients cardiac catheterization can be avoided. Information about the degree of valvular calcification and/or thickening and valve mobility can also be obtained (16). However certain potential sources of error must be recognized (18). Very irregular mitral orifices and the presence of marked valvular calcification may make it difficult to accurately recognize mitral orifice boundaries. In addition limitations in lateral resolution may prevent the precise calculation of small orifice areas (18).

With aortic stenosis aortic valve areas cannot be calculated in the same manner as mitral valve areas since the aortic valve orifice is usually not fully visualized. Weyman has shown that in children the degree of aortic cusp

cardial cushion normally the tricuspid valve is situated to the patient's right and inserts more apically than does the mitral valve. With ventricular inversion since the atrioventricular (AV) valves are also inverted the tricuspid valve again inserts more apically but now is seen to the patient's left (25). In patients with AV canal there is absence of the endocardial cushion and therefore a common level of AV valve insertion (25). Absence of the interventricular septum with a common ventricle can also be appreciated (25). Large ventricular septal defects may be seen as defects in the interventricular septum; however, smaller defects can often be missed depending on their size and location. It is disappointing that despite good visualization of the interatrial septum it is difficult to correctly predict the presence of secundum atrial septal defects. Many normal patients may have dropout of interatrial septal echoes and therefore one must still rely on the features of right ventricular volume overload to suggest the diagnosis.

Transposition of the great arteries (TGA) is best assessed in the short axis plane at the level of the great vessels. Normally in that plane the aorta is seen as a central circular structure with the right ventricular outflow tract and proximal pulmonary artery seen as a sausage-shaped structure curving around the aorta anteriorly. In patients with TGA both great vessels are seen as circular structures with the aorta being anteriorly placed (26, 27). Occasionally this latter pattern may be encountered in patients without TGA and it is therefore useful to try and follow the anterior vessel to its bifurcation establishing it as the pulmonary artery (25). Other conotruncal abnormalities can also be detected. With Tetralogy of Fallot an enlarged right ventricle with overriding of the aorta is seen and in some patients the ventricular septal defect and pulmonic stenosis may be detected. With double outlet right ventricle no great vessel can be seen originating from the left ventricle in any view (25).

The rapid peripheral intravenous injection of normal saline through a narrow bore needle produces highly echo-reflective microbubbles that can be followed through the venous circulation (28). Using this technique the presence of right to left shunting can be detected and its level determined particularly using the apical four chamber view. Prolonged reflux of microbubbles across the tricuspid valve often implies tricuspid regurgitation.



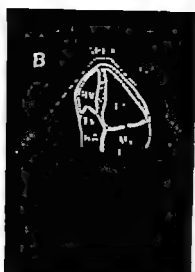


Fig 5 Panel A is a stop-action frame taken in the apical four chamber plane and demonstrates a normal study Panel B is the corresponding line diagram TV = tricuspid valve IAS = interatrial septum other abbreviations as in fig 1

prior to M-mode echocardiography and even cineangiography in the detection of small mass lesions. We have surgically confirmed the detection of intracardiac tumors as small as 1 cm (23). In patients with infective endocarditis (fig 4) it is valuable to serially follow changes in vegetation size as well as to monitor cardiac chamber size and left ventricular performance. Increase in vegetation size or cardiac decompensation while on appropriate medical therapy probably warrants early surgical intervention.

Great care must be taken to avoid overdiagnosis. Experience aids in the distinction between what is clearly abnormal and what is artifact. True mass lesions should be detectable in both long and short axis planes and their exact position localized. The presence of significant valvular calcification or reverberations from prosthetic valves may make it difficult to determine whether mass lesions are present. The intraoperative insertion of sutures or patches may make it difficult to distinguish postoperative superimposed clot unless serial changes can be demonstrated. Left atrial clots cannot reliably be detected and artifacts may sometimes be seen in normal patients, although usually they are seen in only one plane. True atrial myxomas can be recognized by the fact that the great majority can be shown to attach to the interatrial septum in either the short axis or apical four chamber view.

#### CONGENITAL HEART DISEASE

Two-dimensional echocardiography is a valuable tool in the diagnosis of congenital heart disease. It is particularly useful in the diagnosis of congenital heart disease. It is particularly useful in the diagnosis of congenital heart disease. It is particularly useful in the diagnosis of congenital heart disease.

th congeni-  
is cri-  
few  
t  
rs

cardial cushion normally the tricuspid valve is situated to the patient's right and inserts more apically than does the mitral valve. With ventricular inversion since the atrioventricular (AV) valves are also inverted the tricuspid valve again inserts more apically but now is seen to the patient's left (25). In patients with AV canal there is absence of the endocardial cushion and therefore a common level of AV valve insertion (25). Absence of the interventricular septum with a common ventricle can also be appreciated (25). Large ventricular septal defects may be seen as defects in the interventricular septum; however, smaller defects can often be missed depending on their size and location. It is disappointing that despite good visualization of the interatrial septum it is difficult to correctly predict the presence of secundum atrial septal defects. Many normal patients may have dropout of interatrial septal echoes and therefore one must still rely on the features of right ventricular volume overload to suggest the diagnosis.

Transposition of the great arteries (TGA) is best assessed in the short axis plane at the level of the great vessels. Normally in that plane the aorta is seen as a central circular structure with the right ventricular outflow tract and proximal pulmonary artery seen as a sausage-shaped structure curving around the aorta anteriorly. In patients with TGA both great vessels are seen as circular structures with the aorta being anteriorly placed (26, 27). Occasionally this latter pattern may be encountered in patients without TGA and it is therefore useful to try and follow the anterior vessel to its bifurcation establishing it as the pulmonary artery (25). Other conotruncal abnormalities can also be detected. With Tetralogy of Fallot an enlarged right ventricle with overriding of the aorta is seen and in some patients the ventricular septal defect and pulmonic stenosis may be detected. With double outlet right ventricle no great vessel can be seen originating from the left ventricle in any view (25).

The rapid peripheral intravenous injection of normal saline through a narrow bore needle produces highly echo-reflective microbubbles that can be followed through the venous circulation (28). Using this technique the presence of right to left shunting can be detected and its level determined particularly using the apical four-chamber view. Prolonged reflux of microbubbles across the tricuspid valve often implies tricuspid regurgitation.

## CONCLUSION

Two-dimensional echocardiography is still in its infancy. It has been available only for a short period of time and its use has been confined to a limited number of laboratories. Despite this, two-dimensional echocardiography has already been established as an important diagnostic tool with widespread clinical application. Its potential is truly exciting. However, the enthusiasm generated by this new technique must be tempered by the knowledge of its pitfalls and potential limitations. While the technique is non-invasive, a good deal of harm can result from erroneous diagnosis. The method is used optimally when addressing a specific clinical problem. Conclusions should be drawn only when good data are available for analysis. Therefore, the practitioner must compulsively try to obtain the highest quality studies possible. This can only be done if one is familiar with the basic principles of two-dimensional ultrasound, has a clear understanding of three-dimensional cardiac anatomy, and has the technical proficiency gained only by doing a large number of studies. The ability to obtain accurate quantitative data may be limited by inappropriate methodology, inadequate lateral resolution, the level of gain settings, the presence of valvular calcification, and obliquity of the scanning echo beam to the true plane desired.

Again, it must be remembered that the technique is still young. Improvements in instrument design, resolution capabilities, and image processing will lead to even more precise information. Its full potential has not yet been defined. Exciting new areas of investigation include the combined use of transcutaneous Doppler ultrasound and two-dimensional echocardiography to determine cardiac flow (29). Also, sophisticated computer analysis of returning echo signals may provide important clues to underlying tissue histopathology (30). The future of two-dimensional ultrasound appears bright indeed.

## ACKNOWLEDGEMENT

*The authors gratefully acknowledge the assistance of Elaine Rakowski, Dorothy McCain, and Gretchen Selzer in the preparation of this manuscript. This work was supported in part by NIH Grant No HL-5866. Dr Rakowski was supported by an Ontario Heart Foundation Research Fellowship.*

## REFERENCES

- 1 EDLER I and HERTZ C H The use of ultrasonic reflectoscope for the continuous recording of heart walls Kung Fysiofr Sällskap i Lund Förhandl 24 5 1954
- 2 EDLER I and GUSTAFSSON A : Ultrasonic cardiogram in mitral stenosis Acta Med Scand 159 85 1957
- 3 FEIGENBAUM H WALDHAUSEN J A and HYDE L P Ultrasound diagnosis of pericardial effusion JAMA 191 107 1965
- 4 WOLFE S B POPP R L and FEIGENBAUM H Diagnosis of atrial tumors by ultrasound Circulation 39 615 1969
- 5 FEIGENBAUM H Echocardiography Lea & Febiger Philadelphia 1976
- 6 POPP R L and HARRISON D C The use of ultrasound in clinical diagnosis In Non-Invasive Techniques in Cardiac Evaluation Ed A M Weissler Grune and Stratton New York 1974
- 7 KISSLO J A von RAMM O T and THURSTONE F L Cardiac imaging using a phased array ultrasound system II Clinical technique and application Circulation 53 262 1976
- 8 KISSLO J A ROBERTSSON D GILBERT B W VON RAMM O T and BEHAR Y S A comparison of real time two-dimensional echocardiography and cineangiography in detecting left ventricular asymmetry Circulation 55 134 1977
- 9 WEYMAN A E PESKOE S M WILLIAMS E S DILLON J C and FEIGENBAUM H Detection of left ventricular aneurysms by cross sectional echocardiography Circulation 54 936 1976
- 10 RAKOWSKI H MARTIN R P SCHAPIRA J N WEXLER L SILVERMAN J F CIPRIANO P R GUTHANER D F and POPP R L Left ventricular aneurysm Detection and determination of resectability by two dimensional ultrasound (Abstract) Circulation Suppl (In press)
- 11 WEYMAN A E FEIGENBAUM H DILLON J C JOHNSTON K W and EGGLETON R C Noninvasive visualization of the left main coronary artery by cross sectional echocardiography Circulation 54 169 1976
- 12 MARTIN R P FRENCH J W PITTMAN M M and POPP R L : Analysis of idiopathic hypertrophic subaortic stenosis by wide angle phased array echocardiography Circulation 53 11 191 1976 (abstract)
- 13 RAKOWSKI H BOUGHNER D R SOLE M J and WIGLE E D The echocardiographic diagnosis of amyloid cardiomyopathy Circulation 53 (supp II) 11-84 1976 (abstract)
- 14 POPP R L MARTIN R P FRENCH J W and PITTMAN M M Positional distribution of pericardial effusion by real time two-dimensional echocardiography Circulation 53 (supp II) : II 234 1976 (abstract)
- 15 HENRY W L GRIFFITH J M MICHAELIS L L MCINTOSH C L MORROW A G. and EPSTEIN S E Measurement of mitral orifice area in patients with mitral valve disease by real time two-dimensional echocardiography Circulation 51:827 1975

- 16 NICHOL P M GILBERT B W and KISSLO J A Two-dimensional echocardiographic assessment of mitral stenosis *Circulation* 55 120 1977
- 17 WANN L S WEYMAN A E DILLON J C FEIGENBAUM H Determination of mitral valve area by cross sectional echocardiography *Amer J Cardiol* 39 278 1977 (abstract)
- 18 MARTIN R P RAKOWSKI H KLEIMAN J H and POPP R L Is the catheter passé? Limitations of two-dimensional echocardiography for measurement of mitral valve area *Circulation Suppl* (in press) (abstract)
- 19 WEYMAN A E FEIGENBAUM H HURMITZ R A GIROD D A and DILLON J C Cross-sectional echocardiographic assessment of the severity of aortic stenosis in children *Circulation* 55 773 1977
- 20 FEIGENBAUM H WEYMAN A E and DILLON J C Cross sectional echocardiographic visualization of the stenotic pulmonary valve *Amer J Cardiol* 39 279 1977 (abstract)
- 21 GILBERT B W SCHATZ A VON RAMM O T BEHAR V S and KISSLO J A Mitral valve prolapse Two dimensional echocardiographic and angiographic correlation *Circulation* 54 716 1976
- 22 RAKOWSKI H MARTIN R P and POPP R L Two-dimensional echocardiographic findings in mitral valve prolapse *Circulation Suppl* (in press) (abstract)
- 23 MARTIN R P RAKOWSKI H KLEIMAN J H and POPP R L Ultrasonic sector scanning as an alternative or adjunct to cardiac angiography *Amer J Cardiol* 39 278 1977 (abstract)
- 24 SCHILLER N B and SILVERMAN N H Apex echocardiography A new method of imaging the adult heart using a phased array real time two-dimensional 80° sector scanner *Amer J Cardiol* 39 279 1977 (abstract)
- 25 FRENCH J MARTIN R RAKOWSKI H and POPP R L Wide angle ultrasonic scanning A complement to angiography in complex congenital heart disease *Circulation Suppl* (in press) (abstract)
- 26 HENRY W L MARON B J GRIFFITH J M REDWOOD D R and EPSTEIN S E Differential diagnosis of anomalies of the great arteries by real time two-dimensional echocardiography *Circulation* 51 283 1975
- 27 FRENCH J W SILVERMAN N H MARTIN R P SCHILLER N and POPP R L Examination of operative patients with canotruncal abnormalities using an ultrasonic wide angle scanner *Circulation* 54 (suppl II) II-46 1976 (abstract)
- 28 SENARD J B TAJIK A J HAGLER D J and RITTER D G Peripheral venous contrast echocardiography *Amer J Cardiol* 39 202 1977
- 29 HENRY W L and GRIFFITH J M A doppler-cross sectional echocardiographic system for measuring phasic blood flow in man *Circulation* 54 (suppl II) II-152 1976 (abstract)
- 30 JOYNT L BOYLE D RAKOWSKI H POPP R L and BEAVER W Identification of tissue parameters by digital processing of real-time ultrasonic clinical data Presented at the Ultrasonic Tissue Characterization Symposium Washington D C 1977

# TECHNICAL ASPECTS OF SINGLE TRANSDUCER ECHOCARDIOGRAPHY

M S NIEMINEN

*From the Cardiovascular Laboratory University Central Hospital  
Helsinki Finland*

## SUMMARY

In echocardiographic recordings optimal amplification and A-mode control should be used. In wall motion analysis greater accuracy is obtained by utilization of enlarged display scale. When these technical aspects are taken into consideration accurate and reproducible recordings are obtained.

---

## INTRODUCTION

In echocardiography the investigator has to know the chief principles of registration, construction of his equipment, as well as the basis of piezoelectric physics, in order to understand the sensitivity of recordings. Moreover, one has to know the actual sizes of the anatomical sites from which he is recording, being aware of the beam width and lateral dispersion of the ultrasonic beam used.

Accurate measurements of the anatomical structures are obtained using optimal amplification as well as A-mode control in directioning the beam. The accuracy of the measurements, when utilizing enlarged display scale, will also be greater than by 1:1 scale.

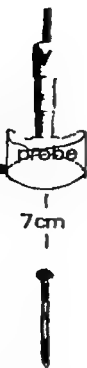
By proper beam selection (enlarged scale, optimal amplification and utilization of A-mode control), recording the left ventricular regional wall motion from several anterior and posterior left ventricular wall locations, which cover almost the entire left ventricle, is possible.

## BEAM SELECTION

The shape of the ultrasonic beam can be influenced in order to improve the scanning accuracy and to obtain more distinct M-mode recordings from predetermined target areas. The divergence in the smaller transducers can be diminished by collimating or focusing the ultrasound beam. Wide and or collimated

position (x,y)  
changed by  
3mm steps

registered  
central and  
disperse  
echoes from  
a nail top in  
10 step grid



0	0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0	0
0	0	1	3	10	8	2	0	0	0
0	0	4	20	33	33	13	1	0	0
3	2	6	55	42	42	24	2	0	0
0	0	9	24	47	47	31	2	1	0
0	0	7	30	45	44	36	6	1	0
0	0	0	1	10	10	16	2	0	0
0	0	0	0	1	2	1	0	0	0
0	0	0	0	0	0	0	0	0	0



Fig 1 Demonstration of the absolute intensities of a 2 MHz plane transducer ultrasound beam when the probe was moved by a micromanometer in 10-step grid to and fro over a head of a nail in water bath. The recorded intensities are tabled on the left. Below the actual values of intensities are drawn the intensity curves of the axial beam. The slight lateral dispersion of this wide transducer is easily deleted by reject set

ated transducers are convenient i.e. when recording regional wall motions of the left ventricle as they provide an uniform and wider axial beam

In an illustrative experiment the axial sound intensity and width of the ultrasound beam of a 2 MHz half an inch transducer was recorded using the head of a nail at 7 cm depth as an absolute reflector. The intensities of reflections were recorded from each step moving the transducer in a 10 step grid to and fro as well as from left to right over the nail head (Fig 1). It was then possible to draw the transversal intensity curves of the axial ultrasound. The lateral dispersion at this depth is also demonstrated which by using proper reject level will be avoided. The experiment also illustrates that the axial intensity of the beam of this plane transducer is quite uniform although highest in central direction. When using a focused transducer the intensity would be even higher in the center while with a narrower transducer the lateral dispersion would be greater. A half inch plane transducer with a surface area of  $1.5 \text{ cm}^2$  and a quite uniform beam intensity is suitable as for example collimated transducers for studying larger cardiac structures e.g. left ventricular regional wall motion, left ventricular diameters, left atrium and the mitral valve. It provides a greater reference area of selected wall region and is thus more reliable for repeated wall motion studies. With a greater axial beam area the same anatomical site is registered with increased probability.

The narrower and more accurate beam is obtained when the beam is focused by a converging lens. These sharper beams are suitable for studying cardiac valves

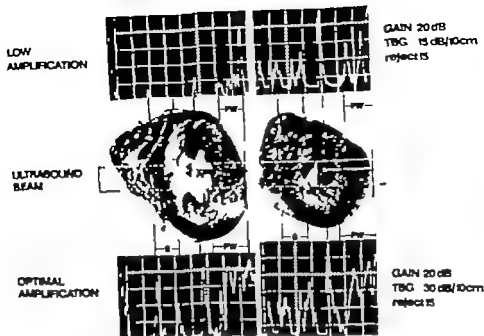


Fig 2 Description of the Ultrasound beam traversing two slices of left ventricle when the left ventricular wall echoes were recorded from an excised heart in a water bath. The head of a nail fixed to two different positions of the posterior wall was used as reference reflector. Formation of the echoes was photoed while the beam was held stationary using low (above) and optimal (below) amplification. In contrast to the distinct echoes even with low amplification from the smooth septal wall high time bound gain (TSG) is required, in order that both the trabecular wall echoes and the trabecular posterior wall echoes are visualized.

Such transducers are usually provided by 5 cm focus radius for children and a 7.5 or 10 cm focus radius for adult studies

#### BEAM PROCESSING

The reflected echoes are weak because the difference of propagation impedance of ultrasound from blood to muscle is very small. Therefore all echoes require amplification to be visualized.

The overall gain with the dynamic range of 11 to 100 dB usually amplifies all echoes similarly. The required overall gain in younger patients is small (15 - 30 dB) but can be twice as high in older subjects with a rigid chest wall (25 - 50 dB). A larger overall gain is also required in obese patients. Because of decibel-wise amplification and attenuation there is remarked difference between anterior and posterior wall echoes approximately from 20 to 30 dB.



position (x,y)  
changed by  
3mm steps

registered  
central and  
disperse  
echoes from  
a nail top in  
10 step grid



0	0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0	0
0	0	1	3	10	8	2	0	0	0
0	0	4	20	35	33	13	1	0	0
3	2	6	35	41	42	26	2	0	0
0	0	9	24	47	47	31	2	1	0
0	0	7	40	45	44	36	6	1	0
0	0	0	1	30	30	16	2	0	0
0	0	0	0	1	2	1	0	0	0
0	0	0	0	0	0	0	0	0	0



Fig 1 Demonstration of the absolute intensities of a 2 MHz plane transducer ultrasound beam when the probe was moved by a micromanipulator in 10-step grid to and fro over the head of a nail in water bath. The recorded intensities are tabulated on the left below the actual values of intensities are drawn the intensity curves of the axial beam. The slight lateral dispersion of this wide transducer is easily deleted by reject set

ated transducers are convenient i.e. when recording regional wall motions of the left ventricle as they provide an uniform and wider axial beam

In an illustrative experiment the axial sound intensity and width of the ultrasound beam of a 2 MHz half an inch transducer was recorded using the head of a nail at 7 cm depth as an absolute reflector. The intensities of reflections were recorded from each step moving the transducer in a 10 step grid to and fro as well as from left to right over the nail head (Fig 1). It was then possible to draw the transversal intensity curves of the axial ultrasound. The lateral dispersion at this depth is also demonstrated which by using proper reject level will be avoided. The experiment also illustrates that the axial intensity of the beam of this plane transducer is quite uniform although highest in central direction. When using a focused transducer the intensity would be even higher in the center while with a narrower transducer the lateral dispersion would be greater. A half inch plane transducer with a surface area of  $1.5 \text{ cm}^2$  and a quite uniform beam intensity is suitable as for example collimated transducers for studying larger cardiac structures e.g. left ventricular regional wall motion, left ventricular diameters, left atrium and the mitral valve. It provides a greater reference area of selected wall region and is thus more reliable for repeated wall motion studies. With a greater axial beam area the same anatomical site is registered with increased probability.

The narrower and more accurate beam is obtained when the beam is focused by a converging lens. These sharper beams are suitable for studying cardiac valves.

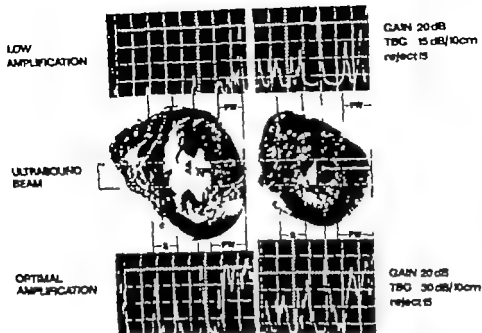


Fig 2 Description of the ultrasound beam traversing two slices of left ventricle when the left ventricular wall echoes were recorded from an autopsied heart in a water bath. The head of a nail fixed to two different positions of the posterior wall was used as reference reflector. Formation of the echoes was photoed while the beam was held stationary using low (above) and optimal (below) amplification. In contrast to the distinct echoes even with low amplification from the smooth septal wall high time based gain (TGC) is required in order that both the muscular wall echoes and the trabecular posterior wall echoes are visualised.

Such transducers are usually provided by 5 cm focus radius for children and a 7.5 or 10 cm focus radius for adult studies

#### BEAM PROCESSING

The reflected echoes are weak because the difference of propagation impedance of ultrasound from blood to muscle is very small. Therefore all echoes require amplification to be visualized.

The overall gain with the dynamic range of 0 to 100 dB usually amplifies all echoes similarly. The required overall gain in younger patients is small (15 - 30 dB) but can be twice as high in older subjects with a rigid chest wall (25 - 50 dB). A larger overall gain is also required in obese patients. Because of decibel-wise amplification and attenuation there is remarked difference between anterior and posterior wall echoes approximately from 20 to 30 dB.

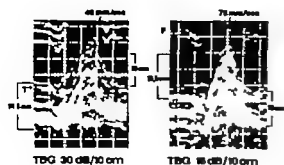


Fig 3 The effect of time bound gain (TBG) to add the trabecular posterior wall echoes to the myocardial thickness during systole. When optimal TBG is utilized reliable values of wall thickness, systolic contraction velocity and motion amplitude can be recorded (left). With low amplification (TBG) the trabecular echoes do not appear in diastole but become gradually visible during systole (right). P = papillary muscle, T = trabeculation echoes.

This difference is corrected by time bound gain (TBG) which is the change of gain with time to compensate for the loss of echo amplitude because of greater attenuation at greater depth. The amount of TBG amplification is gradually added up to the overall gain as a function of time. The required TBG is usually from 20 to 30 dB over a distance of 10 cm. Then, despite attenuation, it is possible to obtain equally strong anterior and posterior wall endocardial and epicardial echoes (fig 2).

However, many spurious echoes arise when maximal TBG is utilized. In motion-mode recordings, these provoke disturbing lines. Therefore, conventional echocardiographic equipment are provided by a reject regulator. When the reject is used, it is important to first recognize the essential echoes so that, e.g., the echoes from the endocardial trabeculations are not deleted. The required reject level in adult studies is usually between 5 to 15 dB (fig 1 & 2).

#### ESSENTIAL ASPECTS IN ECHOCARDIOGRAPHIC RECORDING

In the literature, it has been emphasized that the regional wall motion recordings should be characterized by distinct endocardial and epicardial echolines (2). This could be truly achieved if the myocardium were homogenous tissue. However, the myocardium is constructed of distinct layers and the endocardium is structurally variable, the septal part being rather smooth while other areas are heavily trabeculated (7). The epicardial surface is bordered by a more dense epimyocardial layer. So in fact, a more clear endocardial echo might be seen alone when the gain level is lowered (2) or the reject level is set greater to enable only the strongest echoes to be seen. When this was done (fig 3), the posterior wall echoes were formed solely from the thicker trabeculations or from the first muscular layers behind them. The echoes from the irregularly rough and rounded trabeculations were weak, the ultrasound beam meeting only a small part of the surface of the trabeculae in a straight angle, even weaker than the echoes from the first muscular layers behind them (fig 2).

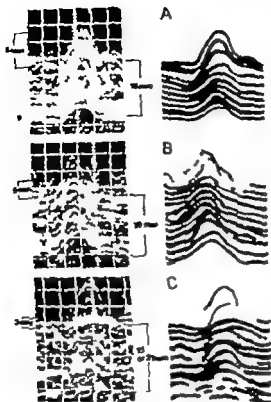
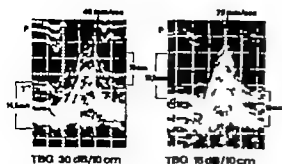


Fig 4: The effect of angulation of the ultrasound beam on the posterior left ventricular wall to measurements of wall thickness and amplitude of motion. A In normal perpendicular registration. B In slight angulation the wall echoes are no more moving parallel throughout the systole. C In extreme angulation the wall echoes cross each other and the variables are severely altered.

With low amplification in the posterior wall recordings the trabeculations cannot be always detected in diastole. In systole however the trabeculations squeeze together forming a much denser surface. The echoes originating from this barrier will then appear in front of the other endocardial echoes. Erroneously high motion amplitudes or systolic wall velocities may then be recorded (fig 3). These difficulties do

however not concern the septal part of the left ventricular anterior wall which has a smooth endocardial surface. Erroneous results in wall motion recordings are also caused by angular directioning of the ultrasound beam towards the wall (fig 4). At an acute angle the wall appears to be thicker since the traversed distance is longer than at straight angle. At an acute angle the echoes do not travel parallel but may intersect because of the axial displacement of the systolic summation echoes originating from the muscular layers. This unparallel motion of wall echoes is best visualized when a larger display scale is utilized in wall motion recordings (fig 3). Abnormal echo-motion caused by the angled direction of the probe can be separated distinctly as the A-mode motion pattern is clearly different from normal.

The right perpendicular direction of the probe is best achieved by slight rotary movements of the probe in the A-mode control. This perpendicular direction is recognized by the maximal amplitude of the endo- and epicardial echoes and the parallel motion of the wall echoes during the cardiac cycle (fig 4). Then



*Fig 3 The effect of time bound gain (TBG) to add the trabecular posterior wall echoes to the myocardial thickness during systole. When optimal TBG is utilized, reliable values of wall thickness, systolic contraction velocity and motion amplitude can be recorded (left). With low amplification (TBG) the trabecular echoes do not appear in diastole but become gradually visible during systole (right). P = papillary muscle. T = trabeculation echoes.*

This difference is corrected by time bound gain (TBG) which is the change of gain with time to compensate for the loss of echo amplitude because of greater attenuation at greater depth. The amount of TBG amplification is gradually added up to the overall gain as a function of time. The required TBG is usually from 20 to 30 dB over a distance of 10 cm. Then despite attenuation it is possible to obtain equally strong anterior and posterior wall endocardial and epicardial echoes (fig 2).

However many spurious echoes arise when maximal TBG is utilized. In motion mode recordings these provoke disturbing lines. Therefore conventional echocardiographic equipment are provided by a reject regulator. When the reject is used it is important to first recognize the essential echoes so that e.g. the echoes from the endocardial trabeculations are not deleted. The required reject level in adult studies is usually between 5 to 15 dB (fig 1 & 2).

#### ESSENTIAL ASPECTS IN ECHOCARDIOGRAPHIC RECORDING

In the literature it has been emphasized that the regional wall motion recordings should be characterized by distinct endocardial and epicardial echolines (2). This could be truly achieved if the myocardium were homogenous tissue. However the myocardium is constructed of distinct layers and the endocardium is structurally variable, the septal part being rather smooth while other areas are heavily trabeculated (7). The epicardial surface is bordered by a more dense epimyocardial layer. So in fact a more clear endocardial echo might be seen alone when the gain level is lowered (2) or the reject level is set greater to enable only the strongest echoes to be seen. When this was done (fig 3) the posterior wall echoes were formed solely from the thicker trabeculations or from the first muscular layers behind them. The echoes from the irregularly rough and rounded trabeculations were weak, the ultrasound beam meeting only a small part of the surface of the trabeculae in a straight angle, even weaker than the echoes from the first muscular layers behind them (fig 2).

TABLE 1 PAIRED OBSERVATION REPRODUCIBILITY

Left ventricle	N	Mean	S D of differences	S E	Significance
Diastolic wall thickness (mm)	34	15.4 <sup>±</sup> 1.0	1.2	0.2	NS
Systolic velocity (mm/sec)	33	41.2 <sup>±</sup> 8.5	2.8	0.5	NS x)
	50	29.6 <sup>±</sup> 21.1	5.0	0.7	NS
Amplitude (mm)	35	9.3 <sup>±</sup> 2.1	0.7	0.1	NS
Diastolic diameter (mm)	39	51.8 <sup>±</sup> 4.5	1.8	0.3	NS

x) one month apart

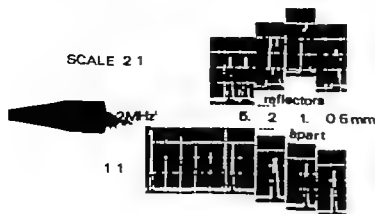
right ventricular junction as well as the apex serve as good anatomical landmarks. The above technical aspects are also important in cross sectional scanings. The advantage of the 2-dimensional real time scanning technique over the single transducer technique is the continuous 2-dimensional visualization and easy anatomical orientation. However in most cases it is difficult to obtain distinct recordings with a sector scanner or linear array system. The single transducer recordings are still more practical in echocardiographic measurements.

### THE REPRODUCIBILITY OF SINGLE TRANSDUCER RECORDINGS

In order to obtain reliable and reproducible data both for acute studies and follow-up recordings standardized scanning technique utilizing anatomical landmarks is required (4,6).

The reproducibility of single transducer recordings by a standard technique (4) were tested in paired observations performed by the same investigator (table 1). The left ventricular wall motion recordings were obtained variably from altogether 8 posterior or anterior wall locations using the echocardiographic technique (4,5). The posterior and anterior wall motion variables as well as the left ventricular end-diastolic diameter were measured from a research series of 39 patients. The investigation was repeated after 10 minutes intermission. A group of normal subjects belonged to a long term follow-up material and the wall motion was recorded with the same standardized technique one month apart. The standard deviation of differences and the standard error of the differences of the paired observations were small and the t test results nonsignificant (table 1). As a conclusion from this

## GREATER ACCURACY BY ENLARGED SCALE



*Fig 5 Demonstration of the enhanced scanning accuracy by utilization of enlarged scale. Two nails were used as point reflectors at a 5 cm distance from the transducer. The returned echoes were registered by 2:1 and 1:1 display scales. The point reflectors were set 0.5, 1.0, 2.0 and 5.0 mm apart. By 2:1 scale it is possible to visualize two different echoes when the nails are only 1 mm apart while by 1:1 scale it is not.*

the true endocardial echoes (echoes from the trabeculations) are recognized among spurious echoes even when high overall gain is required. The A-mode control is best performed in a 2:1 scale (fig 5).

Correlation of the pulsating echo signals to the endocardial and epicardial surfaces can be well seen in the experimental studies and echocardiograms published by Edler and Herz 1961 (1). However, the understanding of the behaviour of the A-mode echoes and their importance in echocardiographic recordings have been mainly neglected because of overemphasis of elegant endocardial and epicardial echoes.

Another important fact to be borne in mind in echocardiographic recordings of left ventricular motion is the slight antero-apical thrust towards the chest wall and the slight anti-clockwise rotation of the heart during the ejection (3). These changes cause regular disturbance in anterior wall motion recordings seen as broken continuity of the systolic echo-lines. A further physiological abnormality is the rounded paradoxical septal motion observed in sportsmen and in subjects with right ventricular dilatation or volume overload (2). The normal character of the M-mode contraction pattern also in these instances may be recognized as normal systolic thickening.

## SINGLE TRANSDUCER OR 2 DIMENSIONAL RECORDING

Taken the above technical aspects in consideration it is possible to obtain accurate single transducer recordings of left ventricular anterior and posterior wall motion from precordial sites using a standardized technique (fig 5, fig 1, ref 5) (6). The different regions cover almost completely the left ventricle thus providing us the possibility to map the left ventricular contraction kinetics (fig 1 in ref 5). For 2-dimensional orientation anatomical reference points are needed, as such mitral valve leaflets (1), aortic root, left and

# THE STUDY OF LEFT VENTRICULAR FUNCTION BY M-MODE ECHOCARDIOGRAPHY

D G GIBSON

*From Brompton Hospital London SW3 6HP*

The first use of echocardiography in studying left ventricular function was to measure the cavity size (1 2) and there is a considerable body of evidence to suggest that reliable estimates of a minor diameter can be made using this method. More recently a second index of left ventricular function the rate of change of dimension has been studied and taken to indicate fibre shortening rate (3 4). Measurements can be made in absolute terms expressed in cm/sec or normalized to refer to unit length of circumference when they are referred to as Vcf or velocity of circumferential shortening. Mean values of shortening rate have been estimated and shown to correlate with corresponding values derived from angiograms in the same patients.

The measurements described above are based on only two determinations of cavity size in each cardiac cycle made at end-systole and end-diastole. Currently available echocardiographs however have a repetition frequency of 1000/sec and so have the potential of studying wall motion continuously with considerably better resolution in time than that available from angiographic methods. Although left ventricular dimension can be measured manually throughout the cardiac cycle this is very laborious and the process can be greatly speeded up using a simple computer technique. In order to do this the echocardiogram to be studied is placed on a digitizing table and a cursor is run along each of the echoes to be measured. The position of the cursor is detected electronically and converted to a series of digital coordinates up to 100 per cardiac cycle being generated for each echo and stored in the computer. This process can be applied to echoes from the right and left sides of the septum the anterior cusp of the mitral valve and endo- and epi-cardial surfaces of the posterior wall. It is also possible to digitize any other continuous signal such as the apexcardiogram or the left ventricular pressure trace. Once these have been digitized the computer can plot them unchanged or can perform further manoeuvres on them. For example the coordinates of the septum can be subtracted from those of



experiment the reproducibility of measurements of wall thicknesses and motion amplitudes is less than 1 mm. The same is true with left ventricular diameters but with greater individual variation. The measurements of the mean systolic motion velocity are subject to greater technical errors in measurement.

## REFERENCES

- 1 EDLER I. Ultrasoundcardiography. Suppl 370 Acta Med Scand 1961
- 2 FEIGENBAUM H. Echocardiography. Lea&Febiger Philadelphia 1971
- 3 MAC DONALD I G. The shape and movement of the human left ventricle during systole. Amer J Cardiol 26 221 1970
- 4 NIEMINEN M S. Applications of multidirectional echocardiography in myocardial infarction. Academic dissertation. Helsinki 1977
- 5 NIEMINEN M S. Heikkilä J. Accuracy and usefulness of echocardiography in acute myocardial infarction. Acta Med Scand
- 6 POPP R L. FILLY K. BROWN O R. HARRISON D C. Effect of transducer placement on echocardiographic measurement of left ventricular diameter. Amer J Cardiol 35 557 1975
- 7 RODBARD S. Structure of the left ventricular myocardium and conduction system. Amer J Cardiol 32 887 1973

# THE STUDY OF LEFT VENTRICULAR FUNCTION BY M-MODE ECHOCARDIOGRAPHY

D G GIBSON

*From Brompton Hospital London SW3 6HP*

The first use of echocardiography in studying left ventricular function was to measure the cavity size (1 2) and there is a considerable body of evidence to suggest that reliable estimates of a minor diameter can be made using this method. More recently a second index of left ventricular function the rate of change of dimension has been studied and taken to indicate fibre shortening rate (3 4). Measurements can be made in absolute terms expressed in cm/sec or normalized to refer to unit length of circumference when they are referred to as Vcf or velocity of circumferential shortening. Mean values of shortening rate have been estimated and shown to correlate with corresponding values derived from angiograms in the same patients.

The measurements described above are based on only two determinations of cavity size in each cardiac cycle made at end-systole and end-diastole. Currently available echocardiographs however have a repetition frequency of 1000/sec and so have the potential of studying wall motion continuously with considerably better resolution in time than that available from angiographic methods. Although left ventricular dimension can be measured manually throughout the cardiac cycle this is very laborious and the process can be greatly speeded up using a simple computer technique. In order to do this the echocardiogram to be studied is placed on a digitizing table and a cursor is run along each of the echoes to be measured. The position of the cursor is detected electronically and converted to a series of digital coordinates up to 100 per cardiac cycle being generated for each echo and stored in the computer. This process can be applied to echoes from the right and left sides of the septum the anterior cusp of the mitral valve and endo- and epi-cardial surfaces of the posterior wall. It is also possible to digitize any other continuous signal such as the apexcardiogram or the left ventricular pressure trace. Once these have been digitized the computer can plot them unchanged or can perform further manoeuvres on them. For example the coordinates of the septum can be subtracted from those of

## NORMAL SUBJECT

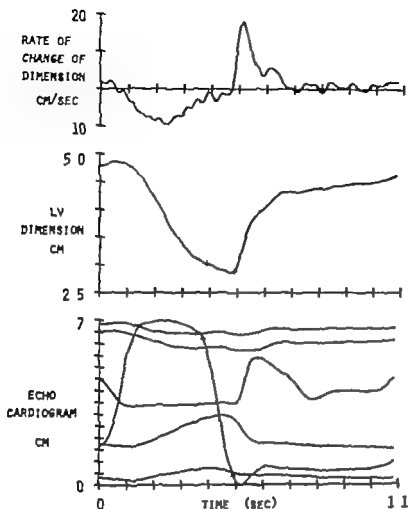
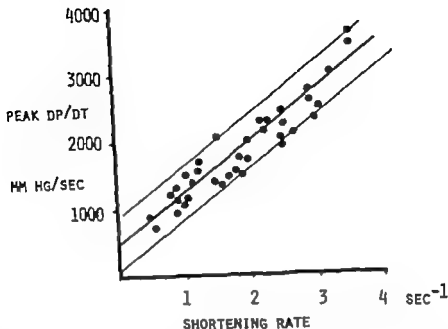


Fig 1 Computer output of left ventricular echocardiogram of a normal subject. The lowest panel represents the digitized data the middle one is a continuous plot of left ventricular dimension and the top shows rate of change of dimension. The two crosses represent the timing of aortic valve closure (A2) and mitral valve opening.

the posterior wall to give a continuous measure of left ventricular dimension or those of endocardium subtracted from those of epicardium to give wall thickness. It is also possible to differentiate a trace with respect to time so that its rate of

change can be calculated. An example of such a plot taken from the echocardiogram of a normal subject is shown in fig 1. The original information is plotted unchanged in the lowest panel. In the middle panel is shown left ventricular dimension which falls during systole and increases rapidly at first during the early phase of ventricular filling and then more slowly during the period of diastasis. The timing of aortic valve closure and mitral valve opening are superimposed as two crosses and it will be seen that there has been little change in dimension during isovolumic relaxation. It is also apparent that mitral valve opening coincides with minimum dimension suggesting that the increase occurring during diastole is indeed due to ventricular filling. Finally the top trace gives the rate of change of dimension which reaches approximately 10 cm/sec during systole and 20 cm/sec during diastole. These estimates of peak rates of wall movement have been compared with corresponding values from angiograms in the same patients and satisfactory agreement obtained (5).



*Fig 2 Relation between simultaneous measurements of peak left ventricular  $dp/dt$  and peak  $Vcf$  in a group of patients with valvular heart disease or cardiomyopathy*

Such measurements of peak rates of wall movement appear to have physiological significance. The relation between peak normalized shortening rate (peak  $Vcf$ ) derived from echo and peak left ventricular  $dp/dt$  measured simultaneously with a micro-manometer in a group of patients with valvular heart disease or cardiomyopathy is shown in fig 2 which demonstrates strong correlation between them. The same relation applies during the immediate postoperative period with such manoeuvres as ventricular pacing or isoprenaline infusion. Discrepancies between them occur in the presence of significant mitral regurgitation when peak  $Vcf$  is greater than would be anticipated from peak left ventricular  $dp/dt$  due to the low impedance pathway for blood flow from the left ventricle. If peak rates of wall movement are to be used as a measure of left ventricular function therefore it is necessary to take the load against which contraction occurs into account.

During filling measurement of continuous rates of change of dimension has proved of clinical value since the normal pattern is modified in the presence of mitral valve disease (7). In mitral stenosis two abnormalities occur: 1. a reduction in the peak rate of increase of dimension to less than 12 cm/sec and 2. prolongation of the period of early diastolic filling measured from the time of minimum dimension to the discontinuity on the dimension

curve representing the onset of diastasis. These abnormalities return towards normal after successful mitral valve surgery. Since it is not the mitral valve itself that is being studied but rather its physiological effects on the left ventricle, the same methods can be applied to patients with mitral prostheses. In addition it is possible to detect valve obstruction or paraprosthetic leak (7).

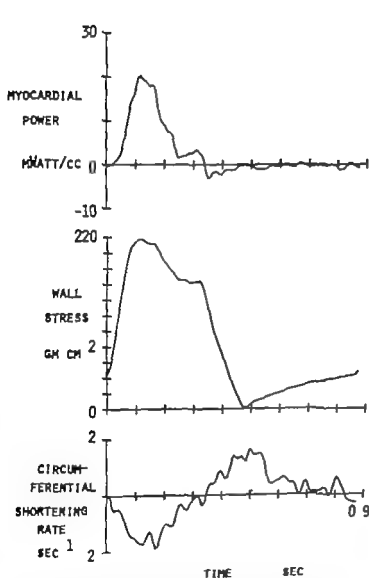


Fig 3 Left ventricular wall stress and shortening rate from a normal subject. The top panel shows myocardial power calculated as the product of wall stress and shortening rate.

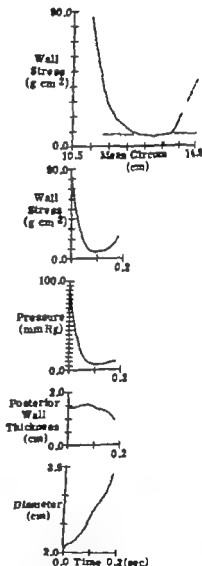


Fig 4 Left ventricular stress-strain relations during diastole. zero time corresponds to minimum dimension. The lowest three panels show changes in dimension, wall thickness and pressure, and above these changes in wall stress with time and (top) the stress-strain relation.

1 Abnormalities of wall movement may also occur in hypertrophic cardiomyo-  
2 pathy in some of whom similar patterns to those of mitral valve disease  
3 may be seen while in others the pattern of filling is normal or even rest-  
4 rictive in character (8). Identical observations have been made angiographi-  
5 cally (9) and both methods show strong correlation between prolonged fill-  
ing and the presence of angina as a prominent symptom. With increasing  
recognition of the significance of diastolic abnormalities in hypertrophic  
cardiomyopathy it is likely that further attention will be given to obser-  
vation of the pattern of wall movement in such patients.

The scope of echo methods can be increased by simultaneously measuring left  
ventricular pressure (6). Knowing left ventricular pressure, dimension  
and wall thickness it is possible to derive wall stress continuously through-  
out the cardiac cycle (fig 3) being based on the simple analytical method  
of Falsetti et al (10). Myocardial power derived as the product of wall  
stress and shortening rate gives a measure of left ventricular contractile  
function which takes resistance to shortening as well as peak rate into  
account. Finally left ventricular diastolic stress-strain relations can  
be studied (fig 4) (11). Such methods take changes in wall thickness into  
account and indicate the complexity of diastolic events even in normal  
subjects.

It seems therefore that the scope of echocardiography in studying left  
ventricular function can be considerably increased by using a simple compu-  
ter technique. Knowledge of peak rates of wall movement may have appreciable  
clinical as well as physiological value and with simultaneous pressure  
measurements a variety of mechanical values can be calculated very much  
less laboriously than by angiography. The presence of incoordinate contrac-  
tion does not preclude their use which is described in detail elsewhere in  
this symposium.

#### REFERENCES

- 1 FORTUIN H J, SHERMAN M E, HOOD W P Jr and CRAIG E  
Evaluation of left ventricular function by echocardiography. *Circulation* 42 111-120 1970.
- 2 FEIGERBAUM H, POPP R L, WOLFE S B, TROY B L, POMBO J F,  
HAINE C L and DODGE H T. Ultrasound measurements of the left  
ventricle: a correlative study with angiography. *Archives of Internal  
Medicine* 126 461 1972.

- 3 PARASKOS J A GROSSMAN W SOLTZ S DALEN J E and DEXTER L  
A non-invasive technique for the determination of the velocity of circumferential fiber shortening *Circulation Research* 29 610 1971
- 4 COOPER R KARLINER J S OIROURKE R A PETERSON K L and LEOPOLD  
■ Ultrasound determination of mean fiber shortening rate in man  
*Amer J of Cardiol* 29 257 1972
- 5 GIBSON D G and BROWN D J Measurement of peak rates of left ventricular wall movement in man *Brit Heart J* 37 677 1976
- 7 ST JOHN SUTTON M G TRAILL T A GHAFOUR A S BROWN D J GIBSON D G  
Echocardiographic assessment of left ventricular filling after mitral valve surgery *Brit Heart J* 39 1823 1977
- 8 SANDERSON J E TRAILL T A ST JOHN SUTTON M G BROWN D J GIBSON D G and GOODWIN J F  
Left ventricular relaxation and filling in hypertrophic cardiomyopathy An echocardiographic study *Brit Heart J* 40 596 1978
- 9 SANDERSON J E GIBSON D G and BROWN D J Left ventricular filling in hypertrophic cardiomyopathy an angiographic study *Brit Heart J* 39 661 1977
- 10 FALSETTI H L MATES R E GRANT C GREENE D G and BUNNELL J L  
Left ventricular wall stress calculated from one-plane cineangiography *Circulation Research* 26 71 1970
- 11 GIBSON D G and BROWN D J Relation between diastolic left ventricular wall stress and strain in man *Brit Heart J* 36 1066 1974

# INFLUENCE OF PHARMACOLOGIC INTERVENTION AND VALVULAR HEART DISEASE ON LEFT VENTRICULAR EJECTION PHASE IN- DICES A REVIEW

A D HAGAN

*From the Clinical Investigation Center Naval Regional Medical Center  
San Diego California.*

## ABSTRACT

Echocardiography represents an established noninvasive technique to evaluate left ventricular (LV) performance. The LV ejection phase indices may be divided into three categories: (1) volume-dependent (2) circumferential and (3) wall thickening. Since the latter two are not volume dependent they are clinically more useful in patients with dilated left ventricles. These parameters have limited clinical value in the presence of left-sided volume overload conditions (e.g. mitral regurgitation and aortic regurgitation) since significant LV dysfunction may exist in the presence of normal ejection phase indices by echo. The echocardiogram is also a sensitive procedure to detect subtle alterations in LV function following acute or chronic interventions with various types of vasoactive and inotropic drugs.

---

Echocardiography has become accepted as a useful clinical parameter for the determination of left ventricular function. Although the unique noninvasive features of this method to evaluate left ventricular performance make it attractive, certain limitations have been recognized. Echocardiographic measurements can be repeated without risk in the same patient as desired, and the ventricular volume and function indices can be followed serially through the natural course of the disease. Even though the accuracy of echo techniques has been well established, the methods are less reliable when the left ventricle has been dilated or when areas of segmental wall motion disorders coexist. (3 5 11 12 30 31 34 36)



- 3 PARASKOS J A GROSSMAN W SOLTZ S DALEN J E and DEXTER L  
A non-invasive technique for the determination of the velocity of circumferential fiber shortening *Circulation Research* 29 610 1971
- 4 COOPER R KARLINER J S O'Rourke R A PETERSON K L and LEOPOLD D  
Ultrasound determination of mean fiber shortening rate in man  
*Amer J of Cardiol* 29 257 1972
- 5 GIBSON D G and BROWN D J Measurement of peak rates of left ventricular wall movement in man *Brit Heart J* 37 677 1976
- 7 ST JOHN SUTTON M G TRAILL T A GHAFOUR A S BROWN D J GIBSON D G  
Echocardiographic assessment of left ventricular filling after mitral valve surgery *Brit Heart J* 39 1823 1977
- 8 SANDERSON J E TRAILL T A ST JOHN SUTTON M G BROWN D J GIBSON D G and GOODWIN J F  
Left ventricular relaxation and filling in hypertrophic cardiomyopathy: An echocardiographic study *Brit Heart J* 40 596 1978
- 9 SANDERSON J E GIBSON D G and BROWN D J Left ventricular filling in hypertrophic cardiomyopathy: an angiographic study *Brit Heart J* 39 661 1977
- 10 FALSETTI H L MATES R E GRANT C GREENE D G and BURNELL J L  
Left ventricular wall stress calculated from one-plane cineangiography  
*Circulation Research* 26 71 1970
- 11 GIBSON D G and BROWN, D J Relation between diastolic left ventricular wall stress and strain in man *Brit Heart J* 36 1066 1974

tion of LV volume by echocardiography (34) The final equation was

$$V = \left[ \frac{7.0}{2.4 + D} \right] D^3$$

where V volume

and D internal dimension measured by echo

Because of the non-uniform contraction of the left ventricle in patients with ischemic heart disease as well as the variations in the relationship between the major and minor axis diameters Laiani and Lee from Canada selected a different method to measure cardiac output from the echocardiogram (26). These investigators determined cardiac output by measuring the cross-sectional area of the aortic root X left ventricular ejection time X mean aortic flow velocity X heart rate. They reported this method of derivation to correlate well with Fick determined outputs in the same group of patients. Ejection time is measured from the aortic valve and the systolic closure (A wave to C point) of the anterior mitral valve leaflet was assumed to represent the mean aortic flow velocity. One potential source for error exists since M-mode echo equipment is not capable of displaying simultaneous recordings from both aortic and mitral valves. It must also be remembered that this technique is based upon all patients having normal aortic and mitral valves.

Gould and associates from Seattle Washington have provided a better explanation of contraction of the intact ventricle (19). Their study described the basis for the method to use angiography to quantitate the three separate contributions to overall ventricular performance; namely longitudinal shortening, circumferential shortening and systolic wall thickening. These investigators observed the contribution of each directional component to the total power developed by a mid-wall equatorial element of myocardium to be (1) longitudinal 14% in normal and diseased ventricles (2) circumferential 45% in normal increasing to 55% in dilated ventricles and (3) wall thickening 40% in normal decreasing to 31% in dilated ventricles.

By considering these components to overall LV performance as proposed by Gould et al it contributes to a better understanding of the numerous echocardiographic parameters which have been employed to evaluate LV function.

Although the estimation of left ventricular (LV) muscle mass does not represent one of the ejection phase indices alterations in mass may influence LV performance. Some investigators have found a good correlation between angio and echo derived LV mass (36). Recently Doctors Devereux and Reichek from the University of Pennsylvania have challenged the standard methods for determination of LV internal dimensions posterior wall thickness and ventricular septal thickness (8). These investigators reported a better correlation with postmortem anatomy by excluding the thickness of left septal and posterior wall endocardial echo lines in the LV internal dimension. The determination of left ventricular wall stress has traditionally required angiographic and left ventricular pressure measurements. Brodie and associates from the University of North Carolina have reported a combined hemodynamic echocardiographic technique to measure left ventricular meridional wall stress throughout the cardiac cycle (4). Having validated the accuracy of this technique by comparison with angiographic data these investigators cited the potential advantages including the ability to study wall stress continuously and to assess its response to serial interventions.

The accuracy and reproducibility of determining ventricular wall thickness and mass by echocardiography has been established (36). The major problem in the calculation of left ventricular volumes by the conventional M-mode technique is that only a single dimension is employed to calculate the volume of the three dimensional left ventricle. Two potential problems arise in the clinical situation where heart size and performance may be altered (1) the various formulas which can be applied to determine volumes are less accurate for enlarged ventricles than for normal size hearts and (2) localized areas of wall motion disorders may not be seen or if observed quantitating the effect of these segmental abnormalities upon overall performance may be extremely difficult. Pombo and associates from the University of Alabama employed the cube method to determine ventricular volumes (30). These investigators noted good correlation by angiography and echocardiography in the assessment of LV volumes and end diastole stroke volume and ejection fraction. Other investigators have noted a poor correlation between angiographically and echocardiographically determined volumes in patients with left ventricular asynergy (34). Doctor Teichholz observed the relationship of minor and major axes of the left ventricle over a wide range of volumes to derive a theoretically corrected equation for determina-

tion of LV volume by echocardiography (34). The final equation was

$$V = \left[ \frac{70}{2.4 + D} \right] D^3$$

where V volume

and D international dimension measured by echo

Because of the non-uniform contraction of the left ventricle in patients with ischemic heart disease as well as the variations in the relationship between the major and minor axis diameters Lalani and Lee from Canada selected a different method to measure cardiac output from the echocardiogram (26). These investigators determined cardiac output by measuring the cross sectional area of the aortic root X left ventricular ejection time X mean aortic flow velocity X heart rate. They reported this method of derivation to correlate well with Fick determined outputs in the same group of patients. Ejection time is measured from the aortic valve and the systolic closure (A wave to C point) of the anterior mitral valve leaflet was assumed to represent the mean aortic flow velocity. One potential source for error exists since M-mode echo equipment is not capable of displaying simultaneous recordings from both aortic and mitral valves. It must also be remembered that this technique is based upon all patients having normal aortic and mitral valves.

Gould and associates from Seattle Washington have provided a better explanation of contraction of the intact ventricle (19). Their study described the basis for the method to use angiography to quantitate the three separate contributions to overall ventricular performance namely longitudinal shortening circumferential shortening and systolic wall thickening. These investigators observed the contribution of each directional component to the total power developed by a mid-wall equatorial element of myocardium to be (1) longitudinal 14% in normal and diseased ventricles; (2) circumferential 45% in normal increasing to 55% in dilated ventricles; and (3) wall thickening 40% in normal decreasing to 31% in dilated ventricles.

By considering these components to overall LV performance as proposed by Gould et al it contributes to a better understanding of the numerous echocardiographic parameters which have been employed to evaluate LV function.

There is no way to measure the minor contribution of longitudinal shortening by M-mode echocardiography. Fortunately 85-90% of LV performance can be measured by determining circumferential shortening and wall thickening both of which can be determined by the echocardiogram very well. For the purpose of this presentation I will divide the echo-derived measurements of LV function into three categories

- (1) Volume-dependent indices such as percent ejection fraction (%EF) and stroke volume (SV)
- (2) Circumferential indices which includes the mean rate of circumferential shortening ( $V_{CF}$ ) and Percent fractional shortening (%FS)
- (3) Wall thickening indices which includes the percent systolic thickening of both septum and posterior wall ( $\%WT_S$ ,  $\%WT_{PW}$ ) the velocity of contraction of both walls ( $V_S$ ,  $V_{PW}$ ) and the normalized velocities of the walls

$$\left[ V_S (\text{sec}^{-1}) \quad V_{PW} (\text{sec}^{-1}) \right]$$

Numerous investigators have studied LV performance in the presence of mitral and aortic valve disease (1, 2, 16, 20, 22, 23, 28, 29, 33, 37). The echocardiogram has been utilized not only to evaluate ventricular function in these patients but also to assess the severity of the valvular disease.

Because of the inherent difficulty in consistently recording the valve orifice area in patients with aortic stenosis wall thickness and LV function indices have been studied by echocardiography in order to estimate the severity of the obstruction. This has been potentially very important since no other noninvasive technique is capable of reliably predicting the degree of aortic stenosis nor accurately detecting progression of the obstruction without serial cardiac catheterizations. (13) Hirschfeld and associates from the University of Cincinnati observed significant shortening of the isovolumic contraction time in children ages 5 to 19 years with aortic stenosis compared to normals. (20) McDonald reported limited value of certain echocardiographic measurements in 31 patients with aortic stenosis but no associated heart failure. (28). Two categories of LV function, volume dependent and circumferential indices were normal in these patients. Only after LV failure had occurred did the %EF,  $V_{CF}$  and %FS decline significantly. Of those parameters measured the only abnormality observed in these patients prior to

When the stenosis was mild the wall thickness remained normal; a 20% increase in diastolic wall thickness occurred in those with moderate stenosis and a 44% increase in LV posterior wall thickness was found in patients with severe stenosis (aortic valve area  $< 0.5 \text{ cm}^2$ )

Bennett et al reported an increased end-systolic wall thickness which was proportional to the intraventricular pressure in patients with aortic stenosis (2). The relative wall thickness was determined from the ratio between echocardiographic measurements of end systolic posterior wall thickness and cavity transverse dimension. These investigators derived values for LV pressure in patients with aortic stenosis by using the formula

$$\text{Systolic intraventricular pressure (kPa)} = \frac{30 \times \text{wall thickness}}{\text{transverse dimension}}$$

Peak systolic aortic valve gradients were determined by subtracting the brachial artery systolic pressure derived by sphygmomanometer from the echocardiographic estimates of LV pressure. The peak gradients as well as valve areas compared favorably with the same parameters which were measured at cardiac catheterization. This approach is based upon the observation that given normal left ventricular function the magnitude of concentric LV hypertrophy is determined by wall stress (wall tension per unit of cross sectional area) with wall mass increasing in proportion to left ventricular load until wall stress returns to normal.

Johnson and co-investigators from Children's Hospital in Cincinnati observed echocardiographic findings in 45 children with aortic stenosis and their results varied from data reported by McDonald (23). This group of investigators from Cincinnati found a good correlation between echo-derived percent fractional shortening and valvular gradient measured at the time of cardiac catheterization. When the shortening fraction exceeded 40% the LV aortic peak systolic pressure gradient was greater than 45 mm Hg in all patients except one. Another circumferential LV function index namely  $\dot{V}_{CF}$  was also found to be increased more than 1.55 circumferences/sec in those patients with valve gradients of 45 mm Hg or more.

Glanz and associates employed the methodology of Bennett to evaluate the severity of aortic stenosis in 13 children and adolescents (16). The derived constant (k) was 225.67 mm Hg in this group of patients and the correlation ( $r = 0.92$ ,  $P < 0.001$ ) was excellent between the estimation by echo and the directly measure LV peak systolic pressure.

Experience in our own laboratory has also provided additional data which support the clinical value of the methodology used by Bennett to estimate the severity of aortic stenosis. However, it should be emphasized that these measurements to estimate LV pressure and valve gradient should not be done in the absence of certain clinical history and physical findings. Patients with hypertension, certain forms of primary myocardial disease and hypertrophic cardiomyopathies may have sufficient wall hypertrophy without LV dilatation to create a misleading suggestion that an aortic valvular gradient may exist.

Although there is significant value to be derived from the echocardiogram in judging the severity of aortic stenosis by measuring circumferential and wall thickening indices, the LV function indices in patients with aortic regurgitation have not had a corresponding value. Both volume-dependent and circumferential LV ejection phase indices by echo correlate very closely with the same parameters when measured from the LV angiogram in the left anterior oblique position (22). However, the same correlation does not exist with the right anterior oblique angiographic data in patients with pure aortic regurgitation. The net result is that the ejection fraction, fractional shortening and mean circumferential shortening rate all tend to remain normal in spite of LV dysfunction due to severe aortic insufficiency. In a few individual cases, we have observed minor deterioration of LV function indices in serial studies during a three to four year period. However, a single echocardiogram has not proven to be very useful in predicting the severity of chronic aortic insufficiency or degree of overall LV dysfunction.

The echocardiographic assessment of LV performance in patients with mitral valve disease has been shown to be normal in most cases (29, 33, 37). The left ventricle may be abnormally small in a few cases of severe mitral stenosis (6 of 47 patients) (29). The ejection phase indices are usually normal in patients with mitral regurgitation even in the presence of left heart failure. Accordingly, the severity of myocardial impairment may be underestimated by the echocardiogram. Some investigators have found the well-compensated patients with mitral regurgitation possess supernormal circumferential indices ( $\%FS$  40 to 45 and  $V_{CF}$  1.5 to 1.6 circs/sec) (33, 37).

Doctors Gibson and Brown from London have used echocardiography to measure instantaneous LV dimension and filling rates in patients with mitral valve disease (15). They determined the LV filling rates in normal subjects to be 880 ml/sec with peak filling occurring at .11 sec from onset of diastole.

and 45% of the stroke volume had entered the ventricle within that period. As expected, the filling rates in those patients with mitral stenosis were markedly reduced, averaging 210 ml/sec, and the filling rates in those with mitral regurgitation were increased to 2,400 ml/sec. Furthermore, they observed a significant difference in the peak filling rate of patients with aortic insufficiency compared to those with mitral regurgitation. Those with aortic insufficiency had slower filling rates, approximately 1,600 ml/sec, and only 19% of the stroke volume had entered the left ventricle within 13 sec, compared to 50% of the stroke volume within 10 sec in those patients with mitral regurgitation.

There has been limited clinical application of echocardiography to assess the influence of cardiac drugs on ventricular performance. However, it has been well established that echocardiography is a sensitive technique to measure acute alterations in LV volume, to detect localized changes of wall motion, and to evaluate the effects on myocardial performance of various pharmacologic agents (6, 9, 10, 14, 17, 18, 21, 24, 25, 27, 32). Redwood and associates observed that LV end-diastolic dimension decreased an average of 11.7% and end-systolic dimension an average of 12.7% following sublingual administration of 0.4 mg nitroglycerin in normal subjects (32). Tilting the subjects from a supine to an 80° head-up position caused comparable reductions in transverse LV dimensions as occurred with nitroglycerin. Phenylephrine caused a rise in atrial pressure, decrease in heart rate, and a significant increase in end-diastolic dimension measured by echo. Furthermore, these investigators observed no change in the mean  $V_{CF}$  by tilting or from phenylephrine, but it was increased by nitroglycerin (from  $1.3 \pm 1$  to  $1.7 \pm 1$  circ/sec). These data on phenylephrine is in disagreement with later findings reported by Hirschleifer and associates from San Diego (21). These authors noted a significant decrease in mean normalized  $V_{CF}$  from  $1.38 \pm 0.6$  to  $1.09 \pm 0.6$  circ/sec ( $P < 0.001$ ) in 25 normal volunteers. After augmenting the heart rate with atropine administration, mean normalized  $V_{CF}$  increased from  $1.22 \pm 0.5$  to  $1.38 \pm 0.6$  circ/sec ( $P < 0.001$ ). Respective decreases and increases were also noted in the normalized posterior wall velocity measurements following phenylephrine and atropine. Accordingly, these investigators pointed out that when ultrasound is used for serial assessment of LV performance or monitoring the influence of a given drug, both heart rate and systemic arterial pressure must be considered in view of their independent effect upon LV function.

Goldstein et al from London recently reported the value of using nitroglycerin to assess changes in the LV end-systolic dimension as an index of



regional performance rather than an estimate of overall LV performance (17). Contraction improved in certain hypokinetic segments and increased systolic shortening occurred during exercise following administration of nitroglycerin. Dumesnil and associates from Canada reported similar findings and observed following nitroglycerin that 54 of 103 hypokinetic regions improved (9). These investigators also studied 13 patients after successful bypass surgery and noted that regional ventricular function had become normal in 11 nitroglycerin responsive areas but failed to improve in 21 nitroglycerin nonresponsive regions.

Kerber and co-investigators from the University of Iowa employed ultrasound in open chest anesthetized dogs to assess wall motion disorders produced by coronary artery ligation (24). A significant increase in aneurysmal bulging during isometric contraction occurred with isoproterenol or ouabain administration. However, during the ventricular ejection phase, the mean posterior wall velocity increased with isoproterenol, glucagon, norepinephrine and ouabain.

The clinical usefulness of echocardiography to evaluate the effects of drugs on left ventricular performance has been further demonstrated by Crawford et al (6). They noted an improvement in the circumferential indices in normal subjects following longterm oral digoxin therapy. An analogous study was performed by Gomes and associates in 10 patients with alcoholic cardiomyopathy (18). These investigators noted significant improvement in the mean posterior wall velocity, normalized posterior wall velocity, mean circumferential fiber shortening, and ejection fraction following oral digoxin therapy. The positive inotropic effect and reduced LV afterload in patients having coronary artery disease have been demonstrated by Ferling and associates following rapid intravenous digitalization with ouabain (10).

Evaluating the effects of general anesthesia on left ventricular function is another new application for the echocardiogram. Lendrum et al from Chicago reported significant deterioration of LV performance in children with no heart disease following nitrous oxide and Halothane or Ethrane anesthesia (27).

We have recently concluded a study in our laboratory in which we evaluated in a double-blind fashion the acute effects of 10 mg chewable isosorbide dinitrate (CHIS) in 11 patients with severe chronic left ventricular failure. We elected to measure only the circumferential and wall thickening indices. We elected to measure only the circumferential and wall thickening indices because all patients had signifi-

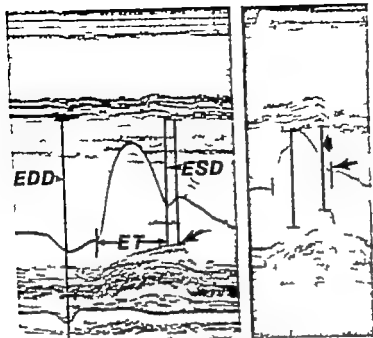


Fig 1 Representative views of the left ventricle with simultaneous carotid pulse recording in two different patients with chronic left ventricular failure showing abnormal septal motion and reduced systolic thickening of the posterior wall in both cases. The patient in the right panel has paradoxical septal motion and the most posterior point during systole occurs in early ejection. The arrow pointing to the second line which precedes the incisura represents the measurement position for the end-systolic dimension (ESD). The left panel shows a patient with an akinetic septum, dilated left ventricle, reduced systolic thickening of the posterior wall with the most anterior peak of the endocardium (arrow) occurring in diastole after the incisura of the carotid pulse. The correct measurement site for the ESD is through the incisura. EDD end-diastolic dimension; ET ejection time.

cant LV dilatation. There was a slight improvement, but not statistically significant, in the circumferential indices following administration of GHIS. However, systolic thickening of the posterior wall was significantly increased following the drug. Because of the severe LV dysfunction and frequent association of paradoxical septal motion, we modified our technique to measure the end-systolic dimension. The incisura of the simultaneous carotid pulse recording, although delayed 20 to 40 msec from actual end-systole, was a more consistent, precise measurement point than either the septal or posterior wall echo reflections. Since the peak anterior point of the posterior wall endocardium was not a reliable marker for end-systole, in fact, it can actually occur in early diastole (fig 1), we determined the end-systolic dimension to be the shortest distance between endocardial surfaces of the septum and posterior wall timed with the incisura of within 40 msec preceding it.

In conclusion echocardiography represents a useful noninvasive technique to evaluate the effect of various pharmacologic agents on left ventricular performance. Furthermore, it is obvious that careful attention must be given to proper recording technique, controlled studies with reproducible measurements and overall quality control. Additional investigations in the field are needed, but it does represent an important method to aid the clinician in weighing potential advantages and disadvantages of cardiac drug regimens.

## REFERENCES

- 1 BACHE R J, WANG Y & GREENFIELD J C. Left ventricular ejection time in valvular aortic stenosis. *Circulation* 47: 527, 1973.
- 2 BENNETT D H, EVANS D W & RAJ M V J. Echocardiographic left ventricular dimensions in pressure and volume overload: their use in assessing aortic stenosis. *Brit Heart J* 37: 971, 1975.
- 3 BENNETT D H & ROWLANDS D J. Test of reliability of echocardiographic estimation of left ventricular dimensions and volumes. *Brit Heart J* 38: 1133, 1976.
- 4 BRODIE B R, MCLAURIN L P & GROSSMAN W. Combined hemodynamic ultrasonic method for studying left ventricular wall stress. *Amer J Cardiol* 37: 864, 1976.
- 5 COOPER R H, O'ROURKE R A, KARLINER J S, PETERSON K L & LEOPOLD G R. Comparison of ultrasound and cineangiographic measurements of the mean rate of circumferential fiber shortening in man. *Circulation* 46: 914, 1972.
- 6 CRAWFORD M H, KARLINER J S & O'ROURKE R A. Favorable effects of oral maintenance digoxin therapy on left ventricular performance in normal subjects: echocardiographic study. *Amer J Cardiol* 38: 843, 1976.
- 7 DE MARIA A N, VISMARA L A, AUDITORE K, AMSTERDAM E A, ZELIS R & MASON D. Effects of nitroglycerin on left ventricular cavity size and cardiac performance determined by ultrasound in man. *Amer J Medicine* 57: 754, 1974.
- 8 DEVEREUX R B & REICHEK N. Echocardiographic determination of left ventricular mass in man: anatomic validation of the method. *Circulation* 55: 613, 1977.
- 9 DUMESNIL J G, LAURENCEAU J L, LABATUT A & GAGNE S. Echocardiographic study of changes in regional ventricular function following nitroglycerin and surgical correlation. *Circulation (suppl II)* 11: 134, 1975.
- 10 FERLING J, DEL VICARIO M & ARONOW W S. Effects of rapid digitalization on left ventricular volumes and asynergy in patients with coronary artery disease: the ouabain ventriculogram. *Amer J Cardiol* 39: 284 (abstr), 1977.

- 11 FORTUIM M J HOOD W P JR SHERMAN M E & CRAIGE E Determination of left ventricular volumes by ultrasound *Circulation* 44 575 1971
- 12 FORTUIM M J HOOD W P JR SHERMAN M E & CRAIGE E Evaluation of left ventricular function by echocardiography *Circulation* 46 26 1972
- 13 FRIEDMAN W F MODLINGER J & MORGAN J R. Serial hemodynamic observations in asymptomatic children with valvular aortic stenosis *Circulation* 43 91 1971
- 14 GOTWIT J CRAWFORD M KARLINER J & O ROURKE II Echocardiographic assessment of left ventricular performance in normal subjects receiving oral quinidine *Circulation* (suppl II) II 191 1975
- 15 GIBSON D G & BROWN D Measurement of instantaneous left ventricular dimension and filling rate in man using echocardiography *Brit Heart J* 35 1141 1973
- 16 GLANZ S HELLENBRAND W E BERMAN M A & TALNER M S Echocardiographic assessment of the severity of aortic stenosis in children and adolescents *Amer J Cardiol* 38 620 1976
- 17 GOLDSTEIN R E BENNETT E D & LEECH G L Effects of nitroglycerin on echocardiographic left ventricular dimensions during upright exercise *Amer J Cardiol* 39 291 (abstr) 1977
- 18 GOMES J A CALDERON J ZAHAM Q MARINO M D & FRIEDMAN H S Improvement in cardiac performance after maintenance digoxin in alcoholic cardiomyopathy an echocardiographic study *Circulation* (suppl II) II-49 1975
- 19 GOULD K L KENNEY J W FRIMER M POLLACK G H & DODGE II T Analysis of wall dynamics and directional components of left ventricular contraction in man *Amer J Cardiol* 38 322 1976
- 20 HIRSCHFELD S MEYER R KORFHAGEN J KAPLAN S & LIEBMAN J The isovolumic contraction time of the left ventricle an echocardiographic study *Circulation* 54 751 1976
- 21 HIRSHLEIFER J CRAWFORD M O ROURKE R A & KARLINER J S Influence of acute alterations in heart rate and systemic arterial pressure on echographic measures of left ventricular performance in normal human subjects *Circulation* 52 (B35-B41) 1975
- 22 JOHNSON A D ALPERT J S FRANCIS G A VIEWEG W V R OCKETTE I & MAGAR A D Assessment of left ventricular function in severe aortic regurgitation *Circulation* 54 975 1976
- 23 JOHNSON G L MEYER R A SCHWARTZ D C KORFHAGEN J & KAPLAN S Left ventricular function by echocardiography in children with fixed aortic stenosis *Amer J Cardiol* 38 611 1976
- 24 KERBER R E ABBUD F H MARCUS M L & ECKBERG D L Effect of inotropic agents on the localized dyskinesia of acutely ischemic myocardium an experimental ultrasound study *Circulation* 49 1038 1974
- 25 KRAJICEK R F & RYAN T J Ultrasound measurements of ventricular wall motion following administration of vasoactive drugs *Amer J Cardiol* 27 464 1971

- 26 LALANI A V & LEE S J K Echocardiographic measurement of cardiac output using the mitral valve and aortic root echo *Circulation* 54 738 1976
- 27 LENDRUM B L ADELMAN D E WONG A CARR I & THORNTON J Echocardiographic determination of the effects of general anesthesia on left ventricular performance *Amer J Cardiol* 39 311 (abstr) 1977
- 28 McDONALD I G Echocardiographic assessment of left ventricular function in aortic valve disease *Circulation* 53 860 1976
- 29 McDONALD I G Echocardiographic assessment of left ventricular function in mitral valve disease *Circulation* 53 865 1976
- 30 POMBO J F TROY B L & RUSSELL R O Jr Left ventricular volumes and ejection fraction by echocardiography *Circulation* 54 480 1971
- 31 QUINONES M A GAASCH W H & ALEXANDER J K Echocardiographic assessment of left ventricular function with special reference to normalized velocities *Circulation* 50 42 1974
- 32 REDWOOD D N HENRY W L & EPSTEIN S E Evaluation of the ability of echocardiography to measure acute alterations in left ventricular volume *Circulation* 50 901 1974
- 33 ROSENBLATT A CLARK R BURGESS J & COHN K Echocardiographic assessment of the level of cardiac compensation in valvular heart disease *Circulation* 54 509 1976
- 34 TEICHHOLZ L E KREULEN T HERMAN M V & GORLIN R Problems in echocardiographic volume determinations echocardiographic-angiographic correlations in the presence or absence of asynergy *Amer J Cardiol* 37 7 1976
- 35 TEN CATE F J KLOSTER F E VAN DORP W G MEESTER G T & ROELANDT J Dimensions and volumes of left atrium and ventricle determined by single beam echocardiography *Brit Heart J* 36 737 1974
- 36 TROY B L POMBO J & RACKLEY C E Measurement of left ventricular wall thickness and mass by echocardiography *Circulation* 45 602 1972
- 37 WANDERMAN K L GOLDBERG M J STACK R S & WEISSLER A M Left ventricular performance in mitral regurgitation assessed with systolic time intervals and echocardiography *Amer J Cardiol* 38 831 1976

# LEFT VENTRICULAR FUNCTION ASSESSMENT BY WIDE ANGLE TWO-DIMENSIONAL ULTRASONIC SECTOR SCANNING

II RAKOWSKI R P MARTIN AND R L POPP

from the Division of Cardiology Stanford University School of Medicine  
Stanford, California

One of the most promising applications of wide-angle two-dimensional echocardiography is the assessment of left ventricular function. The M-mode left ventricular study although useful is somewhat limited by its narrow field of view. Good echocardiographic angiographic correlations for left ventricular volumes and ejection phase indices can be obtained only in patients without significant left ventricular asynergy (1-5). While M-mode echocardiography often can detect regional left ventricular contraction abnormalities particularly of the interventricular septum and posterior wall many wall segments cannot be adequately visualized.

As described in an accompanying paper a prototype and a production model of the Varian V 3000 80° phased array ultrasonoscope has been in clinical use in our laboratory for 18 months. Two-dimensional echocardiography with this wide field of view can provide cross sectional images of the entire long axis of the left ventricle simultaneously. Two-dimensional echocardiography also has the unique ability to image the short axis of the heart in multiple planes from the level of the aorta to the cardiac apex. In this manner all segments of the left ventricle can be seen with correct spatial orientation.

## Qualitative Assessment of Left Ventricular Function Left Ventricular Asynergy

In assessing segmental wall motion abnormalities by two-dimensional echocardiography the left ventricle can be divided into five segments: the interventricular septum, anterolateral wall, posterolateral wall, inferior wall and apex as shown in Fig 1. Combined assessment of long axis and serial short axis views is made. Regional hypokinesis, akinesis or dyskinesis can be detected and its severity can be graded subjectively. Kisslo has shown good correlation between the angiographic and two-dimensional echocardiographic detection of left ventricular asynergy (6) and we have confirmed

Present address: Non Invasive Laboratory Toronto General Hospital  
101 College Street West Toronto Canada

# ANGIOGRAPHY



# TWO-DIMENSIONAL ECHOCARDIOGRAPHY

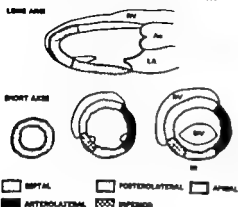


Fig 1 The schema for the correlation of segmental left ventricular contraction abnormalities seen by left ventriculography and two-dimensional echocardiography is shown. The short axis views were taken at the level of the left ventricular apex (I) papillary muscles (II) and mitral valve (III). RAO = right anterior oblique LAO = left anterior oblique LV = left ventricle RV = right ventricle Ao = aorta LA = left atrium MV = mitral valve

this in our laboratory. Since abnormalities of motion are being assessed the optimal method of analyzing these studies is to view them at real time speed. It is difficult to display segmental wall motion abnormalities using stop action single-frame images.

In patients with ischemic heart disease the development of a left ventricular aneurysm can lead to significant clinical deterioration. Since this lesion is potentially surgically correctable its early and accurate detection is of obvious clinical importance. In our limited experience, two-dimensional echocardiography can accurately define the location and size of left ventricular aneurysms with high sensitivity and specificity. This technique has been useful in establishing the diagnosis even when it had not been suggested by physical examination, electro-

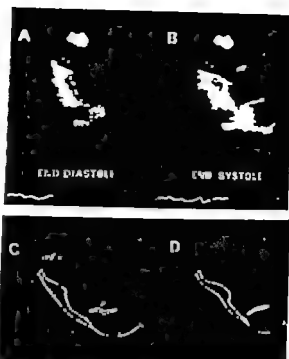


Fig 2 Panels A and B are stop-action frames taken at end-diastole and end-systole in the apical long axis plane. The double white arrows point to the large apical aneurysm which has dyssynchronous systolic motion. Panels C and D are line diagrams corresponding to panels A and B respectively. AN = aneurysm PAP = papillary muscle PW = posterior left ventricular wall LA = left atrium AMV = anterior mitral leaflet LV = left ventricle

A characteristic hinge point was seen in the affected segment beyond which there was aneurysmal bulging of the left ventricular wall with dyskinetic systolic motion (Fig 2). Two-dimensional echocardiography also has proved to be as accurate as angiography in predicting resectability of aneurysms in that the degree of involvement of the papillary muscles and basal segments can be determined. Therefore two-dimensional echocardiography can be used as a reliable non-invasive screening test for left ventricular aneurysms and is especially useful in patients with minimal indications for angiography.

While the detection of asynergy has its greatest clinical application in ischemic heart disease, it is also useful in the assessment of other cardiac disorders. In patients with idiopathic hypertrophic subaortic stenosis the extent of septal hypokinesis and the effects of myectomy can be determined. In some patients with mitral valve prolapse abnormalities of posterobasal left ventricular contraction can be detected and their contribution to the M-mode echocardiographic appearance of prolapse can be assessed. After aortic valve surgery most patients develop hypokinesis of the interventricular septum. Two-dimensional echocardiography allows one to non-invasively follow the natural history of this abnormality and detect whether there is late normalization of wall motion.

In most patients with global left ventricular dysfunction all segments are seen to be equally hypokinetic. Fig 3 is taken from a patient with severe



congestive cardiomyopathy following viral myocarditis. There is little change in ventricular area from end-diastole to end-systole defining the patient's poor ejection fraction.



Fig 3. Panels A and B are stop-action frames taken in the long axis plane at end-diastole and end-systole respectively. Panels C and D are line diagrams corresponding to panels A and B respectively. Note the poor ejection fraction due to the patient's severe congestive cardiomyopathy. RV = right ventricle; IVS = interventricular septum; PW = posterior left ventricular wall; LV = left ventricle; AMV = anterior mitral valve; PML = posterior mitral leaflet; Ao = aorta; LA = left atrium; ECG = electrocardiogram.



## Paradoxical Interventricular Septal Motion

Two dimensional echocardiography has given a clearer understanding of the dynamics of paradoxical interventricular septal motion. Pearlman (7) has suggested that paradoxical septal motion in the presence of normal ventricular activation is not a diagnostic marker for right ventricular volume overload but merely may reflect right ventricular dilatation relative to the left ventricle from any cause. If one assumes that during systole the septum moves toward the center of ventricular mass then the position of the septum at end-diastole determines the direction of systolic motion. If at end diastole the septum is posterior to the center of ventricular mass as can be seen with relative right ventricular dilation its systolic motion will be anterior and therefore paradoxical (7). When these patients are studied using two dimensional echocardiography abnormalities of cardiac geometry and septal motion can be seen with correct spatial orientation. Normally in the long axis plane a septal hinge point is seen separating a small cranial segment that is neutral or has systolic anterior motion from a much larger caudal segment that has posterior systolic motion. Consequently an erroneous diagnosis of paradoxical septal motion may be made on M-mode studies if septal motion is assessed near its attachment to the aortic root. In patients with true paradoxical septal motion there is caudal (apical) displacement of the hinge point therefore most of the septum is moving paradoxically in systole (8). When viewed in the short axis plane the septum is flattened and posteriorly displaced making the configuration of the left ventricle ellipsoid rather than circular (9). In extreme cases there may be frank reversal of the normal diastolic septal curvature giving the kidney shaped appearance of encroachment of the septum into the left ventricular cavity. In such patients with the onset of systole there is rapid septal eversion toward normal circular shape which causes the rapid early systolic anterior septal motion seen with M-mode echocardiography (9). This is illustrated in Fig 4.

## Quantitative Assessment of Left Ventricular Function

Superficially it would seem easy to compare two-dimensional echocardiography with angiography and obtain good correlations of quantitative left ventricular function. Both techniques provide dynamic images of the whole long axis of the left ventricle. Both can display the left ventricle in motion at real time speed or can provide stop-frame images for tracing end diastolic and end systolic ventricular outlines. However there are significant differences between the two techniques that limit comparison. Angiography provides

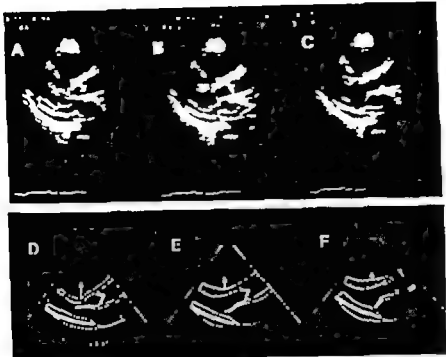


Fig 4: Panels A, B and C are stop-action frames taken in the long axis plane from a patient with severe pulmonary hypertension and pulmonary regurgitation. Panels D, E and F correspond to A, B and C respectively. The right ventricle is markedly dilated with a small left ventricular cavity. The size of the white arrows indicates the magnitude of paradoxically anterior systolic septal motion still to come. Panel A was taken in late diastole. In the isovolumic contraction phase (Panel B) the interventricular septum is already rapidly moving anteriorly and most of the paradoxical motion has already taken place by mid-systole (Panel C). An incidental small posterior pericardial effusion is present. RV = right ventricle; LV = left ventricle; IVS = interventricular septum; PW = posterior left ventricular wall; Ao = aorta; LA = left atrium; PERI = pericardium; EFF = effusion.

A silhouette image of the left ventricle and volumes and ejection phase indices are usually measured using a  $30^\circ$  right anterior oblique projection. In contrast, two-dimensional echocardiography provides a tomographic cross-sectional image which should theoretically give a consistently smaller cavity area than a silhouette projection. In addition, the plane of the cross sectional image of the long axis of the left ventricle is more analogous to a hemiaxial  $60^\circ$  left anterior oblique angiographic projection.

Certain technical limitations of two-dimensional echo systems also must be considered. Left ventricular studies suitable for quantitative analysis can be obtained in only about 80 % of patients. Factors such as obesity and chronic obstructive pulmonary disease may lead to incomplete visualization of the left ventricle. In some patients the only good echo window is found at or just medial to the cardiac apex. The routine use of this apical view maxi-

zes the number of acceptable studies and also helps eliminate the foreshortening of the left ventricle that sometimes can be seen in studies taken from the 3rd and 4th intercostal spaces. With certain abnormalities of cardiac geometry (e.g. left ventricular aneurysm or idiopathic hypertrophic subaortic stenosis) all parts of the long axis of the left ventricle may not lie in the same plane. In these patients two dimensional sector scans may underestimate the true long axis area whereas the angiographic silhouette may provide an overestimation. There are other potential sources of error as well. Significant systolic cardiac motion out of the plane of the scan may occasionally occur so that different parts of the heart are compared in systole and diastole. Also since lateral resolution is only 3 to 5 mm apparent boundaries between the left ventricular cavity and walls may not represent the true endocardial interfaces.

Despite these potential limitations, accurate semiquantitative measurements can be obtained. Wide angle two-dimensional echocardiography can clearly define patients with normal versus abnormal left ventricular volumes and ejection fractions regardless of whether left ventricular asynergy is present. In our experience comparison of quantitative measurements of angiographic and two dimensional echocardiographic data taken from single-plane long axis views of the left ventricle alone do not yield a high correlation. It is not yet clear whether accurate quantitative data are obtainable from current two-dimensional echocardiographic studies. It may be that the method of extracting it has not yet been perfected. The serial short axis views obtained with two-dimensional echocardiography provide unique information about the shape of the left ventricle. We are currently studying the feasibility of combining data from different planes of the left ventricle as well as using several mathematical models of the left ventricle instead of a simple ellipse of rotation. Forthcoming improvements in system signal processing resolution and stop-frame image quality probably also will lead to better quantification of left ventricular function.

#### ACKNOWLEDGEMENT

The authors gratefully acknowledge the assistance of Elaine Rakowski, Dorothy McCain and Gretchen Selzer in the preparation of this manuscript. This work was supported in part by NIH Grant No HL-5868. Dr Popp was supported by a Research Career Development Award No K04-HL-704-39. Dr Rakowski was supported by an Ontario Heart Foundation Research Fellowship.

## REFERENCES

- 1 POPP R L WOLFE S B FEIGENBAUM H Estimation of right and left ventricular size by ultrasound *Am J Cardiol* 24 523 1969
- 2 POPP R L HARRISON D C Ultrasonic cardiac echography for determining stroke volume and valvular regurgitation *Circulation* 41:493 1970
- 3 FORTUJK M J HOOD W P Jr SHERMAN H E CRAIGE E Determination of left ventricular volumes by ultrasound *Circulation* 44 575 1971
- 4 GIBSON D G Estimation of left ventricular size by echocardiography *Brit Heart J* 35 128 1973
- 5 TEICHHOLZ L E KREULEN T Herman M V GORLIN R Problems in echocardiographic volume determinations Echocardiographic angiographic correlations in the presence or absence of asynergy *Am J Cardiol* 37 7 1976
- 6 KISSLO J A ROBERTSON D GILBERT B W VON RAMM O T BEHAR V S A comparison of real time two-dimensional echocardiography and cineangiography in detecting left ventricular asynergy *Circulation* 55 134 1977
- 7 PEARLMAN A S CLARK C E HENRY W L MORGANTHO J ITSCOVITZ S B EPSTEIN S E Determinants of ventricular septal motion Influence of relative right and left ventricular size *Circulation* 54 83 1976
- 8 KAGAN A D FRANCIS G S SAHN D J KARLINER J S FRIEDMAN W F O'Rourke R A Ultrasound evaluation of systolic anterior septal motion in patients with and without right ventricular volume overload *Circulation* 50 248 1974
- 9 WEYMAN A E WARD S FEIGENBAUM H DILLON J C Mechanism of abnormal septal motion in patients with right ventricular volume overload A cross sectional echocardiographic study *Circulation* 54 179 1976

zes the number of acceptable studies and also helps eliminate the foreshortening of the left ventricle that sometimes can be seen in studies taken from the 3rd and 4th intercostal spaces. With certain abnormalities of cardiac geometry (e.g. left ventricular aneurysm or idiopathic hypertrophic subaortic stenosis) all parts of the long axis of the left ventricle may not lie in the same plane. In these patients two dimensional sector scans may underestimate the true long axis area whereas the angiographic silhouette may provide an overestimation. There are other potential sources of error as well. Significant systolic cardiac motion out of the plane of the scan may occasionally occur so that different parts of the heart are compared in systole and diastole. Also since lateral resolution is only 3 to 5 mm apparent boundaries between the left ventricular cavity and walls may not represent the true endocardial interfaces.

Despite these potential limitations accurate semiquantitative measurements can be obtained. Wide angle two dimensional echocardiography can clearly define patients with normal versus abnormal left ventricular volumes and ejection fractions regardless of whether left ventricular asynergy is present. In our experience comparison of quantitative measurements of angiographic and two dimensional echocardiographic data taken from single plane long axis views of the left ventricle alone do not yield a high correlation. It is not yet clear whether accurate quantitative data are obtainable from current two-dimensional echocardiographic studies. It may be that the method of extracting it has not yet been perfected. The serial short axis views obtained with two-dimensional echocardiography provide unique information about the shape of the left ventricle. We are currently studying the feasibility of combining data from different planes of the left ventricle as well as using several mathematical models of the left ventricle instead of a simple ellipse of rotation. Forthcoming improvements in system signal processing resolution and stop-frame image quality probably also will lead to better quantification of left ventricular function.

#### ACKNOWLEDGEMENT

The authors gratefully acknowledge the assistance of Elaine Rakowski, Dorothy McCain and Gretchen Selzer in the preparation of this manuscript. This work was supported in part by NIH Grant No. HL-5886. Dr. Popp was supported by a Research Career Development Award No. K04-HL-704-39. Dr. Rakowski was supported by an Ontario Heart Foundation Research Fellowship.

## METHODS

Patients Left ventricular wall motion was studied by real time two-dimensional echocardiography and biplane cineventriculography in 105 consecutive patients undergoing diagnostic cardiac catheterization for a variety of clinical problems. Mean  $\pm$  standard deviation ages was  $47 \pm 11$  (range 15 to 72).

Echocardiographic Methods Two-dimensional echocardiograms were performed on all patients using a previously described (1,2) real time phased-array imaging system. All two-dimensional echocardiograms were obtained on the day prior to cardiac catheterization according to previously described techniques (2). Cross sectional images of the left ventricle were obtained in the long axis of the left ventricle and in serial short axis views at the levels of the mitral valve tips of the papillary muscles, bodies of the papillary muscles and apex.

In an attempt to closely approximate the true short axis of the left ventricle, the transducer was placed perpendicular to the chest wall and the ventricle was scanned until the image of the left ventricle appeared most circular in configuration. Particular care was taken to avoid extreme transducer angulation as it distorted the appearance of the ventricular circumference (oval rather than circular) and made the interpretation of ventricular geometry and asynergy unreliable.

Catheterization Methods All patients underwent complete left and right heart catheterization from the right groin using the Seldinger technique. Biplane left ventricular cineangiograms were obtained in the orthogonal left and right anterior oblique projections. Cineangiograms were recorded on 35 mm film at a speed of 60 frames per second.

Data Analysis Ventricular wall motion was classified as either normal or abnormal in each of five echocardiographically and angiographically determined wall regions (anterolateral, posterolateral, septal, inferior and apical). Abnormal systolic wall motion was defined according to the terminology of Herman et al (3). The echocardiograms and cineventriculograms were analyzed by two independent groups of investigators, neither having knowledge of the other's conclusions until the time of data correlation. To serve as a basis for comparison, the echocardiographic results were used to predict the appearance of the biplane cineventriculogram in each patient. The echocardiogram was then judged as correct or incorrect in identifying the ventricular wall motion characteristics as determined by angiography. In this way, a total of 525 potential wall regions were analyzed by each method. After initial correlation, both echocardiograms and angiograms were reviewed by the combined investigative teams to determine the reasons for agreement or disagreement.

# EVALUATION OF THE LEFT VENTRICLE BY TWO-DIMENSIONAL ECHOCARDIOGRAPHY

J A KISSLO

*From the Department of Medicine Cardiovascular and Clinical Cardiology Laboratories Duke University Medical Center Durham North Carolina USA*

## SUMMARY

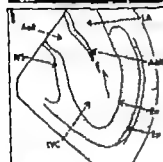
Left ventricular wall motion was assessed in 105 consecutive patients both invasively using biplane cineangiography and non-invasively by a real-time phased-array two-dimensional echocardiography system. Ventricular wall motion in five anatomic areas of the ventricle (anterolateral posterolateral apical septal and inferior) was analyzed by both methods in a double-blind manner. Two-dimensional echocardiographic images were deemed adequate for analysis in 82 % of the regions (430 of 525). Fifty-five discrepancies were noted in the comparison of the remaining 430 regions.

The reasons for discrepancies in interpretation between the two methods were established for 54 during retrospective review: 33 were due to echocardiography (inadequate target visualization, observer error, or tangential echo views). Fifteen were related to angiography (overlay of silhouettes or observer error) and six were due to other reasons including definition problems or spatial orientation difficulties.

Both real-time two-dimensional echocardiography and cineangiography have advantages and disadvantages. The techniques used together could provide more complete information concerning ventricular wall movement than is now currently available.

## INTRODUCTION

Real time two-dimensional echocardiography is a relatively new approach to visualizing cardiac dynamics. At present there is little available information regarding the utility of this method for the detection of ventricular asynergy. In this study the results of the assessment of ventricular wall motion by two-dimensional echocardiography were compared to similar data obtained by biplane cineventriculography. This comparison was used to define the interrelationships between the two techniques.



**Echocardiographic Angiographic Correlations** In all 105 patients biplane ventriculograms were considered adequate for the analysis of wall motion. Eighteen percent (95 of 525) of wall regions however could not be visualized by two-dimensional echocardiography. It should be noted that in the 430 regions visualized by echocardiography wall motion characteristics were correctly identified in 87% (375 of 430). Discrepancies between the echocardiographic and angiographic findings occurred in 13% (55 of 430).

Fig 2 Stop-frame mid-diastolic image and schematic diagram through the long axis of the left ventricle in a 90 degree sector are shown. There is mild ventricular dilatation and virtually the entire left ventricle is seen from aortic root to apex. Endocardium. The remainder of the abbreviations are the same as in Fig 1.

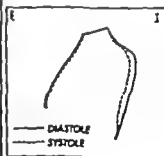
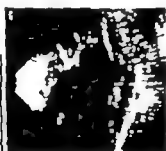
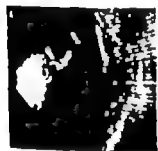


Fig 2. Sequential diastolic (A) and systolic (B) stop-frame scan images in the 90 degree sector are shown through the long axis of the left ventricle of a patient with coronary artery disease and a huge ventricular aneurysm. The corresponding schematic diagrams (C and D) have been added. Panel E demonstrates diffuse asynergy with relative preservation of motion along the posterior wall region at the base of the heart. LVA left ventricular aneurysm. Remainder of abbreviations are the same as in Fig 1.



## RESULTS

**Correlative Examples** Figure 1 shows stop frame systolic images through the long axis and two short axis views of the left ventricle from a patient with a normally contracting left ventricle. Figure 2 demonstrates the advantage of the 90 degree sector arc since this wide field of view occasionally allowed for visualization of the entire left ventricle in long axis.

The two-dimensional echo and angiographic findings of a patient with a ventricular aneurysm are shown in fig 3 and 4. While the two-dimensional echo demonstrated normal wall motion of the posterior region of the heart, this was difficult to appreciate in the ventriculogram due to superimposition of the large opacified aneurysm on the remainder of the ventricular silhouette.

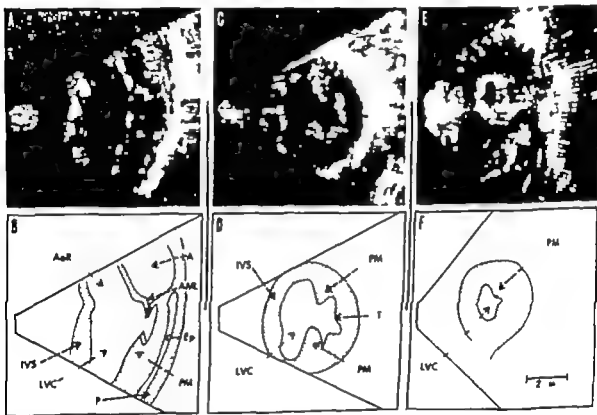


Fig 1 Stop-frame systolic images and schematic drawings through the ventricular long axis (Panels A and B), short axis at the papillaries (Panels C and D), and short axis at the apex (Panels E and F) from a patient with a normally contracting left ventricle and mild mitral prolapse. Scans in Panels A and C are in the 50 degree sector arc while the scan in Panel E is in the 90 degree sector arc. Note that the left ventricle is normally circular in configuration when viewed in short axis (C and D). Several endocardial trabeculations can also be seen in Panel C. AoR = aortic root, LA = left atrium, ANL = anterior mitral leaflet, Ep = epicardium, PM = papillary muscle, P = pericardium, LVC = left ventricular cavity, IVS = interventricular septum, T = trabeculation.

includes unresolved disagreements between the echocardiographic and angiographic interpretations. The indeterminate discrepancies included only mild abnormalities and in two instances the asynergy noted in a specific region by echocardiography was seen in an adjacent wall region by angiography.

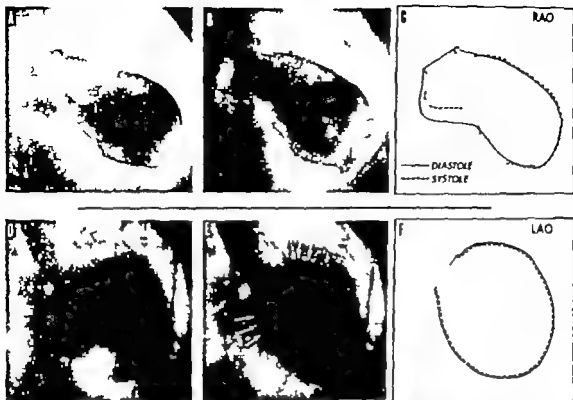
Discrepancies due to observer error and inadequate target visualization by echo were most frequently encountered in the interpretation of apical wall motion while problems experienced with the ventricular silhouette on angiography were encountered most frequently in interpreting septal wall motion.

Adequacy of Echo Targets Since the double-blind analysis revealed that inadequate endocardial echo targets accounted for the most frequent error by echocardiography, the echocardiograms were carefully reviewed in an effort to establish minimal criteria for assessing the adequacy of an echo image. Upon review, it was clear that at least 50% of the endocardium in any one wall region must be visualized throughout the cardiac cycle in order to reliably predict the presence or absence of asynergy. Visualization of all regions of the left ventricle by two-dimensional echocardiography was possible in 60% of these patients while failure to visualize any of the regions occurred in 11%. The most readily visualized regions were the septal and posterior walls while the most difficult region to visualize was the ventricular apex.

## DISCUSSION

Proper echocardiographic technique is most important in obtaining a true cross-sectional image of the left ventricle. Even though this difficulty was well recognized before this study was begun, 7% of the discrepancies noted on double-blind analysis were due to improper echo technique. The heart as a constantly moving three dimensional target is rotating in and out of the interrogating plane during the cardiac cycle. An improperly directed transducer causes the scan plane to intercept the ventricular cavity tangentially and may result in distortion of normal ventricular configuration and wall motion. When the ventricle is viewed in long axis, this problem is most easily recognized when the normal elliptical configuration of the cavity appears circular or cut-off near the origins of the papillary muscles. When the ventricle is viewed in short axis, this problem is recognized when the cavity appears oval rather than circular in shape.

Eighteen percent of the discrepancies noted were due to echocardiographic observer error and resulted from two basic problems that were heretofore unrecognized in the interpretation of two dimensional echocardiographic images.



*Fig 4 Sequential diastolic (A and D) and systolic (B and E) angiographic frames from the same patient pictured in Fig 3. The RAO view is pictured on the top row while the LAO view is on the bottom. Note the large ventricular aneurysm and contracting base in Panel C. The arrows in Panel E point to the contracting base that is poorly visualized through the silhouette of the aneurysm in the LAO view (Panel F). These findings were similar to those predicted by two-dimensional echocardiography.*

**Discrepancy Analysis** In order to fully appreciate the interrelationships between two dimensional echocardiography and angiography, the data was then retrospectively reviewed. Suspected reasons for 54 of the 55 discrepancies were identified and classified. Of the 34 discrepancies attributable to echocardiography, ten were due to observer error and 19 were due to inadequately visualized echo targets that were previously judged as adequate. Despite the care taken to properly position the transducer on the chest wall, four errors were caused by tangential angulation of the transducer through the short axis of the ventricular cavity resulting in distortion of wall movement.

The majority of the 15 discrepancies due to angiography resulted from the superimposition of abnormally contracting wall regions over the normally contracting portions of the ventricle (Fig 4). For example, when severe anterior wall asynergy was present, the abnormally contracting anterior wall was superimposed over the interventricular septum in LAO angiographic view, thus obscuring true septal wall motion.

The six discrepancies termed indeterminate were so classified because they could not readily be attributed to either imaging technique. This category

includes unresolved disagreements between the echocardiographic and angiographic interpretations. The indeterminate discrepancies included only mild abnormalities and in two instances the asynergy noted in a specific region by echocardiography was seen in an adjacent wall region by angiography.

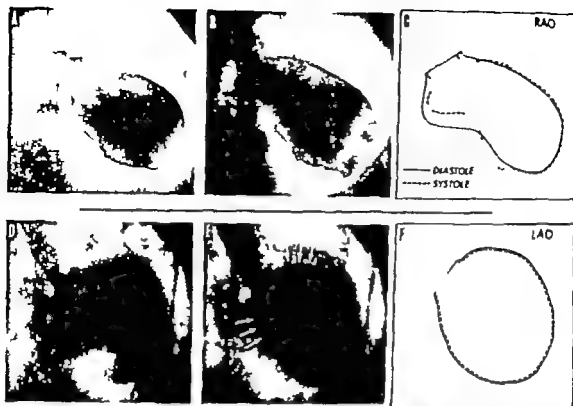
Discrepancies due to observer error and inadequate target visualization by echo were most frequently encountered in the interpretation of apical wall motion while problems experienced with the ventricular silhouette on angiography were encountered most frequently in interpreting septal wall motion.

Adequacy of Echo Targets Since the double-blind analysis revealed that inadequate endocardial echo targets accounted for the most frequent error by echocardiography, the echocardiograms were carefully reviewed in an effort to establish minimal criteria for assessing the adequacy of an echo image. Upon review, it was clear that at least 50% of the endocardium in any one wall region must be visualized throughout the cardiac cycle in order to reliably predict the presence or absence of asynergy. Visualization of all regions of the left ventricle by two-dimensional echocardiography was possible in 60% of these patients while failure to visualize any of the regions occurred in 11%. The most readily visualized regions were the septal and posterior walls while the most difficult region to visualize was the ventricular apex.

## DISCUSSION

Proper echocardiographic technique is most important in obtaining a true cross-sectional image of the left ventricle. Even though this difficulty was well recognized before this study was begun, 7% of the discrepancies noted on double-blind analysis were due to improper echo technique. The heart as a constantly moving three dimensional target is rotating in and out of the interrogating plane during the cardiac cycle. An improperly directed transducer causes the scan plane to intercept the ventricular cavity tangentially and may result in distortion of normal ventricular configuration and wall motion. When the ventricle is viewed in long axis, this problem is most easily recognized when the normal elliptical configuration of the cavity appears circular or cut-off near the origins of the papillary muscles. When the ventricle is viewed in short axis, this problem is recognized when the cavity appears oval rather than circular in shape.

Eighteen percent of the discrepancies noted were due to echocardiographic observer error and resulted from two basic problems that were heretofore unrecognized in the interpretation of two dimensional echocardiographic images.



*Fig 4 Sequential diastolic (A and D) and systolic (B and E) angiographic frames from the same patient pictured in Fig 3. The RAO view is pictured on the top row while the LAO view is on the bottom. Note the large ventricular aneurysm and contracting base in Panel C. The arrows in Panel E point to the contracting base that is poorly visualized through the silhouette of the aneurysm in the LAO view (Panel F). These findings were similar to those predicted by two-dimensional echocardiography.*

**Discrepancy Analysis** In order to fully appreciate the interrelationships between two dimensional echocardiography and angiography, the data was then retrospectively reviewed. Suspected reasons for 54 of the 55 discrepancies were identified and classified. Of the 34 discrepancies attributable to echocardiography, ten were due to observer error and 19 were due to inadequately visualized echo targets that were previously judged as adequate. Despite the care taken to properly position the transducer on the chest wall, four errors were caused by tangential angulation of the transducer through the short axis of the ventricular cavity resulting in distortion of wall movement.

The majority of the 15 discrepancies due to angiography resulted from the superimposition of abnormally contracting wall regions over the normally contracting portions of the ventricle (Fig 4). For example, when severe anterior wall asynergy was present, the abnormally contracting anterior wall was superimposed over the interventricular septum in LAO angiographic view, thus obscuring true septal wall motion.

The six discrepancies termed indeterminate were so classified because they could not readily be attributed to either imaging technique. Is ca

Since this study deals with the correlation of data from two distinctly different imaging techniques it is not surprising that discrepancies occurred that could readily be attributed to both echocardiography and angiography. It is most important to realize that the two techniques working together could potentially provide more complete information concerning ventricular wall movement than is now available.

#### ACKNOWLEDGEMENT

This work was supported in part by USPHS Grants HL-18716 HL-14828 HL-17670 and ES-01818

#### REFERENCES

- 1 YOM RAHM OT THURSTONE FL Cardiac imaging using a phased array ultrasound system I System design Circulation 53 258 1976
- 2 KISSLO J YOM RAHM OT THURSTONE FL Cardiac imaging using a phased-array ultrasound system II Clinical technique and application Circulation 53 262 1976
- 3 PERMAN HY GORLIN R Implications of left ventricular asynergy American J Cardiol 23 538 1969

First as the heart contracts in systole it rotates and moves in an inferior and anterior direction. When the left ventricle is viewed in its short axis by echocardiography, therefore, this systolic descent and anterior motion appeared to reduce the visually apparent posterior motion of the septum induced by ventricular contraction. Second, several observer errors were made when the 50 degree sector scan format was utilized and the entire ventricular circumference in short axis was not included in the field of view. Because of this incomplete visualization, the relative motions of the various wall regions were not fully appreciated and failure to recognize minor to moderate degrees of asynergy resulted. Although a short axis scan through a normal size ventricle usually includes the entire ventricular wall in a 50 degree sector arc, such is not the case when the ventricle is dilated. As wide a field as possible, therefore, should be employed when examining the left ventricle for asynergy.

Proper judgment concerning the adequacy of an echocardiographic image for interpretation of left ventricular asynergy is clearly most important since 35 % of the discrepancies noted were due to the inadequacy of the echocardiographic image. In retrospect, it appeared that assessment of wall motion characteristics of a specific wall region could be reliably attempted only when at least 50% of the endocardium in any one wall region is visualized throughout the cardiac cycle. It was encouraging that all five heart wall regions could be visualized using this criterion in 60% of the patients examined. It should be kept in mind, however, that the most difficult wall regions to visualize were the apical, inferior and anterolateral. Such findings are not surprising since target drop out (loss of targets due to tangential angulation to the echo beam) and/or interfering lung tissue are most often encountered when attempting to image these specific wall regions.

The fact that 27% (15 of 55) of the discrepancies noted were attributable to angiography indicates that cineventriculography, as any other technique, has certain limitations. Paramount among these is the superimposition of the silhouette of an abnormally contracting wall segment over one that is normal, making detection of the normal motion occasionally difficult or impossible. For similar reasons, most of the ventricular wall surfaces are inaccessible to radiographic contrast imaging techniques since the only motion detected by this method is on the border of the visualized silhouette. Biplane cine ventriculography, of course, tends to reduce these sources of misinterpretation. Since this technique is invasive, its application is limited to relatively small numbers of patients selected for cardiac catheterization.

subvalvular portion of the outflow tract (1) In addition outflow obstruction may occur at multiple levels as the common association of coarctation of the aorta and bicuspid aortic valve illustrates (2 3)

Correct characterization of obstruction requires that one recognize the presence and severity of the lesion as well as its location in the outflow tract and morphologic type When obstruction is present at one level it is also important to be able to evaluate the remainder of the outflow tract to rule out associated lesions M-mode echocardiography has been variably successful in detecting the morphologic type extent and severity of lesions producing obstruction to left ventricular outflow (4 5) In some types of obstruction such as IHSS the M-mode technique has been extremely valuable permitting the diagnosis (6 7) severity (8) response to therapy (9) and inheritance pattern of the disease to be examined (10 11) In other areas such as congenital valvular aortic stenosis (12 14) the M-mode technique has been notably unreliable

Much of the difficulty with the M-mode method is due to the tubular nature of the outflow tract The M-mode beam can only reflect obstruction or narrowing of this cylindrical structure by recording a change in outflow tract diameter during continuous scanning from one region to another Recording a change in diameter may be difficult to evaluate; however since apparent decrease in diameter may result from eccentric beam angulation while an artifactual increase in diameter occurs when the beam is scanned obliquely along the long axis of the vessel

Cross sectional echocardiography by enlarging our field of vision generally permits the entire area of obstruction to be encompassed within the plane of the scan This allows comparison of the area of obstruction with the more normal outflow tract proximal and distal to this region In addition more precise characterization of the morphology and extent of the lesion and in certain cases its severity is possible In this report we will review our experience using the cross-sectional echocardiographic system to detect and characterize areas of obstruction to left ventricular outflow Consideration of these lesions will begin at the superior portion of the outflow tract in the region of the aortic arch and progress down the outflow tract through the region of the aortic valve into the left ventricle

## AORTIC OBSTRUCTION

### A. Coarctation of the Aorta

It is well established that by placing the M-mode transducer in the supra



# CROSS-SECTIONAL ECHOCARDIOGRAPHIC ASSESSMENT OF AORTIC OBSTRUCTION

A E WEYMAN

*From the Kanner Institute of Cardiology the Department of Medicine  
Indiana University School of Medicine and the Veterans Administration  
Hospital Indianapolis Indiana*

## SUMMARY

Cross-sectional echocardiographic features of aortic obstruction occurring at multiple levels of the left ventricular outflow tract are described. Specific pathologic entities considered include coarctation of the aorta, supravalvular, valvular, and discrete subvalvular aortic stenosis, as well as functional or idiopathic hypertrophic subaortic stenosis. At each of these levels the cross-sectional method permits direct visualization of the obstructing lesion, its morphologic characteristics, and extent. In addition, the relationship of the area of obstruction to more normal surrounding areas of the outflow tract can be assessed. Studies at the supravalvular and valvular levels indicate the direct imaging of the stenotic area may permit estimation of severity.

At the subvalvular level the patterns of development of functional obstruction can be examined and the mechanisms of this type of obstruction further elucidated. Finally, in addition to direct visualization of individual areas of obstruction, it is possible to detect or exclude areas of concomitant obstruction at other levels of the outflow tract. Cross-sectional echocardiography therefore represents a rapid, non-invasive method for visualizing the location, extent, severity, and dynamic nature of lesions producing obstruction to left ventricular outflow.

---

Obstruction to left ventricular outflow may be either congenital or acquired. The obstruction may result from a fixed anatomic area of narrowing or be functional, varying with the physiologic state of the patient (e.g., IHSS). Although obstruction occurs most commonly at the level of the aortic valve, it may be located in the aorta distal to the valve or in the

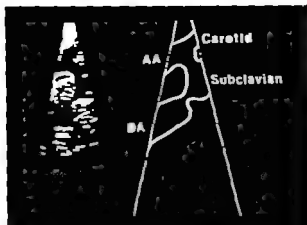


Fig 2 Cross-sectional scan of the distal aortic arch and proximal descending aorta from a patient with coarctation of the aorta. There is a localized area of discrete aortic narrowing distal to the origin of the left subclavian artery. At the level of maximal obstruction there appears to be almost complete obliteration of the vascular lumen. Distal to the area of obstruction the aorta returns to the relatively normal luminal diameter.

Fig 3: Angiogram corresponding to the cross-sectional study in Figure 2. In this recording there is again a localized area of constriction or coarctation of the aorta distal to the origin of the left subclavian artery. The similarity in appearance of the obstructing lesion by both these imaging techniques is apparent.



main relatively parallel throughout the area of the scan. In a recent study (18) to evaluate the ability of cross sectional echocardiography to record anatomic changes in the proximal descending aorta in patients with coarctation it was observed that the distal aortic arch and descending aorta could be visualized in 16 of 18 patients examined. In each of these 16 patients there was a localized area in which the echoes from the walls of the aorta protruded into the aortic lumen producing partial constriction or obstruction of the vessel. In each case there was a similarity between the echocardiographic location and appearance of the lesion and the location and morphology of the coarctation at angiography.

Fig 2 is a cross sectional recording from a patient with coarctation of the aorta. In this figure there is marked inward bending of the echoes from the medial and lateral walls of the descending vessel distal to the origin of the left subclavian artery. This shelf of echoes protruding into the vascular lumen produces almost complete obstruction of the vessel at this level. Fig 3 is an angiogram recorded from the same patient demonstrating the presence of an area of coarctation at a level similar to that visualized by the cross sectional recording.



*Fig 1 Diagram illustrating the position of the cross-sectional probe in the suprasternal notch and orientation utilized to record the aortic arch and proximal descending aorta. While recording this region the probe is normally directed inferiorly posteriorly and slightly leftward. The plane of the scan is therefore oriented approximately  $45^{\circ}$  to both the sagittal and coronal planes of the body.*

sternal notch and directing the beam inferiorly one can record echoes from the superior and inferior walls of the aortic arch, the right pulmonary artery and the left atrium (15, 17). Visualization of the distal aortic arch and proximal descending aorta and detection of obstruction or coarctation in this region however has not been possible with the M-mode system. This occurs because the path of the descending aorta is parallel to or directly away from the ultrasonic beam. Because of this orientation the walls of the vessel are poorly recorded and an accurate aortic diameter in this region is unobtainable. Since detection of areas of obstruction requires comparison of the diameter in the narrowed region with that in surrounding normal areas, this inability to accurately record the transverse diameter of the vessel prevents detection of coarctation.

Cross sectional echocardiography, by displaying the derived acoustic data in a spatially oriented format, permits the distal aortic arch and proximal descending aorta to be visualized. Since the walls of the vessel can be imaged, it is possible to estimate the transverse diameter and hence to appreciate changes in this diameter produced by localized obstruction. Fig 1 illustrates the transducer placement and areas encompassed by the  $30^{\circ}$  sector with the plane of the cross sectional scan oriented parallel to the long axis of the descending aortic arch. In normal subjects the descending arch appears as an elongated, tubular, echo-free area which curves leftward and inferiorly away from the scanning transducer. The walls of the vessel re-

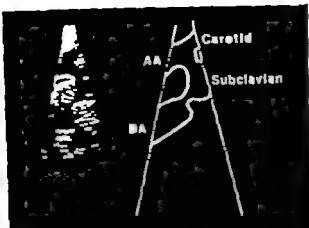


Fig 3 Angiogram corresponding to the cross-sectional study in Figure 2. In this recording there is again a localized area of constriction or coarctation of the aorta distal to the origin of the left subclavian artery. The similarity in appearance of the obstructing lesion by both these imaging techniques is apparent.

Fig 2 Cross-sectional scan of the distal aortic arch and proximal descending aorta from a patient with coarctation of the aorta. There is a localized area of discrete aortic narrowing distal to the origin of the left subclavian artery. At the level of maximum obstruction there appears to be almost complete obliteration of the vascular lumen. Distal to the area of obstruction the aorta returns to the relatively normal luminal diameter.



main relatively parallel throughout the area of the scan. In a recent study (18) to evaluate the ability of cross sectional echocardiography to record anatomic changes in the proximal descending aorta in patients with coarctation it was observed that the distal aortic arch and descending aorta could be visualized in 16 of 18 patients examined. In each of these 16 patients there was a localized area in which the echoes from the walls of the aorta protruded into the aortic lumen producing partial constriction or obstruction of the vessel. In each case there was a similarity between the echocardiographic location and appearance of the lesion and the location and morphology of the coarctation at angiography.

Fig 2 is a cross-sectional recording from a patient with coarctation of the aorta. In this figure there is marked inward bending of the echoes from the medial and lateral walls of the descending vessel distal to the origin of the left subclavian artery. This shelf of echoes protruding into the vascular lumen produces almost complete obstruction of the vessel at this level. Fig 3 is an angiogram recorded from the same patient demonstrating the presence of an area of coarctation at a level similar to that visualized by the cross sectional recording.

In addition to the abnormal anatomic appearance of the arch in patients with coarctation there was also a characteristic change in the pattern of systolic pulsation of the vessel which aided in the detection of coarctation. With coarctation there was very prominent pulsation of the vessel proximal to the area of narrowing. Distal to the area of obstruction the vascular pulsation was markedly decreased. Although similar degrees of pulsation of the aortic arch may be seen in patients with aortic insufficiency and other high output states, the amplitude of pulsation in these disorders is consistent throughout the course of the vessel. The presence of vigorous pulsations of the aortic arch therefore suggests the possibility of coarctation while the marked difference in the amplitude of pulsation in the pre and post obstructive portions of the vessel differentiates this lesion from other disorders associated with prominent arch pulsations.

#### B Supravalvular Aortic Stenosis

Supravalvular aortic stenosis is a congenital obstructive deformity of the aorta which characteristically arises just distal to the coronary arteries and produces either localized or diffuse narrowing of the ascending aorta (19). Although the designation supravalvular stenosis encompasses a heterogeneous group of anatomic lesions, three specific anatomic types have been described. These include the membranous type consisting of a simple fibrous diaphragm containing a single perforation, the hourglass type characterized by extreme thickening of the medial layer of the ascending aorta associated with an hourglass deformity of the external aspect of the vessel and corresponding narrowing of the aortic lumen, and the hypoplastic variety characterized by uniform hypoplasia of the entire ascending aorta.

In a recent study (18) we examined a group of 5 patients with supravalvular aortic stenosis (4 hourglass and 1 hypoplastic) to evaluate the ability of cross sectional echocardiography to visualize the area of obstruction and to determine the severity and extent of the lesion. In each of these cases there was a clearly defined area of decrease in aortic luminal diameter beginning superior to the distal margin of the sinuses of Valsalva and extending to involve a variable portion of the proximal ascending aorta. Fig 4 is a characteristic recording from a patient with supravalvular aortic stenosis. In this recording there is narrowing of the aortic lumen produced by an inward bending of the echoes from the anterior and posterior aortic walls at the junction of the superior border of the sinuses of Valsalva and the more distal ascending aorta. The area of obstruction coin-

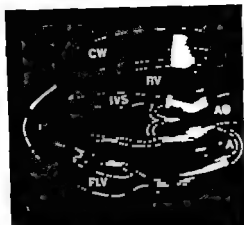


Fig 4: Cross-sectional echogram from a patient with moderately severe supracardiac aortic stenosis of the hourglass variety I this figure there is an area of aortic narrowing or constriction occurring at the level of the junction of the superior margin of the sinuses of Valsalva and proximal ascending aorta. The obstruction is reflected by an inward curvature of the echoes from the anterior and posterior margins of the aortic walls which produces a restriction in luminal diameter. Distal to the area of obstruction there is a gradual increase in aortic diameter.



Fig 5: Angiogram corresponding to the cross-sectional study in Fig 4. Again the area of marked decrease in aortic diameter at the superior margin of the sinuses of Valsalva is evident.

cedes spatially with the superior margin of the left atrium. Distal to the area of obstruction the walls of the aorta gradually separate to return to a more normal luminal diameter. Fig 5 is an angiogram of the ascending aorta from the same patient demonstrating the similarity in location and extent of the obstructing lesion.

In order to determine the ability of the cross sectional echogram to accurately define the size of the aortic lumen at the level of obstruction the aortic diameter at the point of maximal narrowing determined from the cross sectional echogram was compared to the similar value measured from the angiogram. In each of these cases the echocardiographic dimension was within 3 mm of the corresponding angiographic dimension. In addition in 3 of the 4 patients with hourglass type lesions in whom the full extent of the area of obstruction could be recorded by the cross sectional technique the cross sectional estimate of extent of obstruction was within 5 mm of the corresponding angiographic dimension. In the single patient with hypoplasia of the ascending aorta the area of obstruction was felt to involve the entire vessel by both techniques.

Finally due to the normal variability of the outflow diameter between the sinuses of Valsalva and proximal ascending aorta it may be difficult in the individual cases to differentiate normal change in diameter from mild supra-avalvular obstruction. In order to examine this question the variability in outflow tract dimension in a group of 20 normal subjects was compared with that observed in patients with supra-avalvular stenosis. In each of the 20 normal patients the aortic diameter at the aortic annulus was equal to or slightly smaller than the corresponding diameter at the superior margin of the sinuses of Valsalva. In none of these cases did the diameter decrease between these two levels. In contrast in each of the 4 patients with hourglass type lesions the diameter decreased markedly from the aortic annulus to the proximal ascending aorta at the superior margin of the sinuses of Valsalva. This decrease in diameter ranged from 25 to 61 % and in this small group appeared to correlate with the peak systolic gradient at the level of obstruction.

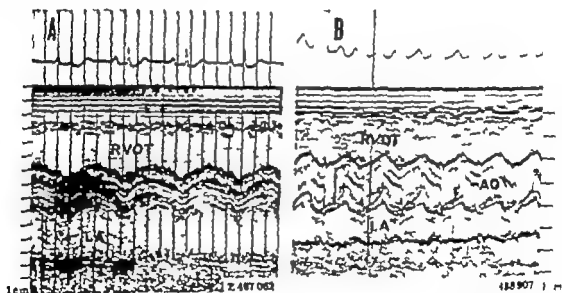


Fig 6 M-mode echocardiographic recording from two patients with valvular aortic stenosis. Panel 6A shows a dense mass of linear echoes recorded from the aortic root with absence of apparent opening of the aortic valve suggesting severe stenosis. At cardiac catheterization however the patient had a very mild valvular lesion. In contrast Panel 6B is a recording from a child with severe valvular aortic stenosis. In this study the aortic leaflet separation and apparent valve opening appeared to be normal. This figure illustrates the problems which occur in attempting to estimate the severity of aortic stenosis from the M-mode record. RVOT=right ventricular outflow tract AOV=aorta LA=left atrium.

Although this is a preliminary study in a relatively small group of patients it does indicate that the cross sectional technique can accurately visualize the supra-avalvular area of the aorta detect obstruction in this region.

determine the degree and morphologic characteristics of the obstructing lesion and by comparing the diameter at the level of obstruction to more normal areas of the outflow tract provide at least a rough estimate of the severity of the obstructing lesion

### C. Valvular Aortic Stenosis

The M-mode echocardiogram has been widely used in an attempt to diagnose valvular aortic stenosis (12 13 14 20). In addition attempts have been made to determine the degree or severity of stenosis based on the density of echo production from the stenotic valve (12) or direct measurement of aortic leaflet separation as a reflection of orifice size (14). While each of these observations has proven helpful in individual cases, it has not been possible to reliably or consistently estimate the severity of aortic stenosis using M-mode echocardiography. Fig 6 is an example of the difficulties encountered in attempting to estimate severity of stenosis from the M-mode record. Panel A is a recording from a patient with calcific aortic stenosis. The dense echo production from the aortic root and absence of recordable leaflet separation suggests severe stenosis; however, at cardiac catheterization this patient had only a mild lesion. This failure to appropriately reflect the severity of the stenotic lesion occurs because the M-mode beam may strike only a localized area of the aortic root recording dense bands of echoes from a region of calcification while failing to visualize an eccentric area of normal leaflet motion. Panel B is a recording from a child with severe congenital valvular aortic stenosis (peak systolic gradient 154 mm Hg). In this figure the aortic leaflets separate widely suggesting apparent normal leaflet motion. Assessment of the presence and severity of the congenitally stenotic valve is an area where the M-mode technique has been notably unreliable (12 14).

This occurs because the narrow M-mode beam transects the base of the domed valve where the leaflets lie perpendicular to the path of the beam and hence present strong reflecting

Fig 7 Long axis cross-sectional echogram from a child with congenital valvular aortic stenosis. This recording illustrates systolic closure of the anterior and posterior aortic cusps together with a marked decrease in aortic valve orifice size (vertical arrow). There is accentuation of the inner margins of the valve cusps at the orifice due to elongation of the echoes from this interface. This apparent artifact is due to the strong reflecting interface at the blood tissue margin which helps to highlight the valve orifice.





Finally due to the normal variability of the outflow diameter between the sinuses of Valsalva and proximal ascending aorta it may be difficult in the individual cases to differentiate normal change in diameter from mild supravalvular obstruction. In order to examine this question the variability in outflow tract dimension in a group of 20 normal subjects was compared with that observed in patients with supravalvular stenosis. In each of the 20 normal patients the aortic diameter at the aortic annulus was equal to or slightly smaller than the corresponding diameter at the superior margin of the sinuses of Valsalva. In none of these cases did the diameter decrease between these two levels. In contrast in each of the 4 patients with hourglass type lesions the diameter decreased markedly from the aortic annulus to the proximal ascending aorta at the superior margin of the sinuses of Valsalva. This decrease in diameter ranged from 25 to 61 % and in this small group appeared to correlate with the peak systolic gradient at the level of obstruction.

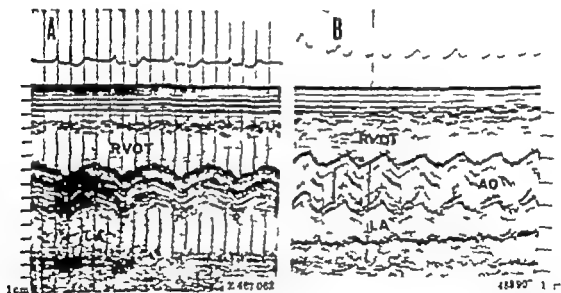


Fig 6 M-mode echocardiographic recording from two patients with valvular aortic stenosis. Panel 6A shows a dense mass of linear echoes recorded from the aortic root with absence of apparent opening of the aortic valve suggesting severe stenosis. At cardiac catheterization however the patient had a very mild valvular lesion. In contrast Panel 6B is a recording from a child with severe valvular aortic stenosis. In this study the aortic leaflet separation and apparent valve opening appeared to be normal. This figure illustrates the problems which occur in attempting to estimate the severity of aortic stenosis from the M-mode record. RVOT=right ventricular outflow tract. AO=aorta. LA=left atrium.

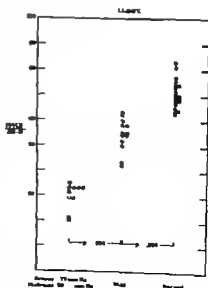
Although this is a preliminary study in a relatively small group of patients it does indicate that the cross sectional technique can accurately visualize the supravalvular area of the aorta, detect obstruction in this region

maximum aortic cusp separations of 11 mm or less had been considered surgical candidates

Measurement of the maximum aortic cusp separation in the same group of patients using the M-mode system revealed several significant differences. First in only 21 of the 28 patients (75%) was it possible to record an aortic valve orifice using the M-mode system. Secondly in one patient with moderately severe non calcific aortic stenosis the M-mode markedly overestimated aortic valve orifice size while in three patients with mild aortic stenosis the M-mode record revealed aortic valve orifices of 10 mm or less suggesting a severe lesion. Thus although it was possible to record the aortic valve orifice in the majority of patients using the M-mode technique in individual cases the derived data was clearly misleading.

A follow up study (22) to determine the ability of this system to record the aortic valve in children revealed that in 93% of a group of 30 consecutive children the aortic valve could be recorded and the valve orifice visualized. Because preliminary data suggested that correction of aortic valve orifice size for body surface area did not adequately relate aortic cusp separation to patient size a ratio was constructed between the maximum degree of cusp separation as a reflection of the actual aortic valve orifice and the aortic root diameter at the level of the aortic annulus as a reflection of potential orifice size. Using this ratio a good correlation was demonstrated between both the peak systolic aortic valve gradient (Fig 9) and the aortic valve area calculated using the Gorlin formula. These two studies suggest that cross sectional echography offers an improved method for the

Fig 9: Diagram illustrating the relationship of maximum aortic cusp separation expressed as a percentage of the aortic root diameter to severity of aortic stenosis in a group of 25 children with valvular aortic stenosis and 22 normal subjects. The left hand column contains children with moderate or severe valvular aortic stenosis (peak systolic aortic valve gradient  $>50$  mm Hg). The middle column contains 13 children with mild valvular aortic stenosis (gradient  $<50$  mm Hg) and the right hand column contains 22 normal patients. (From Weyman AE et al. Cross-sectional echocardiographic assessment of the severity of aortic stenosis in children. *Circulation* 55 773 1977)



surfaces. The apex of the dome where the leaflets lie parallel to the beam is poorly visualized and hence the flow limiting area and true degree of stenosis not appreciated.

Cross-sectional echocardiography by expanding our field of vision and providing correct spatial orientation allows the entire aortic valve to be recorded simultaneously and hence its true shape and motion pattern appreciated (21, 22). Fig 7 is a cross sectional echogram from a child with a congenitally stenotic aortic valve. The cross-sectional system permits visualization of the full spatial configuration of the domed valve as well as the obvious decrease in luminal diameter produced by the diminished valve orifice. Comparing this recording with Panel B in Fig 6 emphasizes

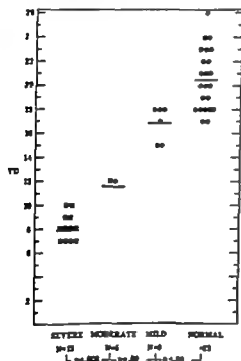


Fig 8 Relationship of maximum aortic cusp separation or aortic valve diameter (AVD) to severity of aortic stenosis in 28 adult patients with valvular stenosis and 25 normal subjects. The squares in the figure indicate patients who were considered to be surgical candidates based on clinical and hemodynamic evaluation. The circles indicate normal subjects and those patients not felt to require aortic valve surgery. (From Heyman AE et al. Cross-sectional echocardiography in assessing the severity of valvular aortic stenosis. *Circulation* 52:838, 1975)

the relative merits of these systems. Similarly in adults by sweeping the plane of the scan from the medial to the lateral surfaces of the aorta it is possible to visualize localized areas of normal leaflet motion and hence to more

appropriately characterize the valve orifice in patients with densely fibrotic or calcific stenotic valves.

In addition to detecting the presence of valvular aortic stenosis it is also possible by measuring the degree of aortic leaflet separation to estimate the severity of the stenotic lesion. In an early study (21) of a group of 28 adult patients with calcific aortic stenosis it was demonstrated that a clear relationship existed between the maximum aortic cusp separation and the severity of stenosis (Fig 8). When this patient group was further examined to determine which patients were recommended for surgery based on clinical and hemodynamic criteria it was found that all patients with

left ventricular outflow tract in 16 patients with discrete subvalvular aortic stenosis and have observed two characteristic patterns of outflow obstruction which correspond to the subgroups noted above (24-25). In addition we have observed a single patient who appears to represent a third pattern of obstruction which differs markedly from either of the groups classically described. In a group of three patients with obstruction produced by localized thin subvalvular membranes two discrete linear echoes were observed in the outflow tract proximal to the aortic valve. These echoes appeared unattached to the anterior or posterior walls of the outflow tract and were felt to be produced by the blood tissue interface of the inner margins of the fibrous membrane. Fig 10 illustrates the cross-sectional appearance of this type of lesion. The two characteristic linear echoes are present at the tip of the horizontal arrow. In these cases there was some dynamic motion of these echoes towards each other during systole. Fig 11 is a cross-sectional recording of a similar patient following surgical resection of the subvalvular membrane. Although there is a small residual echo producing shelf along the posterior margin of the outflow tract the two linear echoes from the membrane itself are no longer present.

In a second group of 12 patients whose subvalvular obstruction was characterized by a more diffuse area of outflow narrowing consistent with subvalvular fibromuscular rings or subvalvular tunnels a second pattern of outflow obstruction was observed. This was characterized by an extensive area of inward bending of the linear echoes from the anterior and posterior wall of the outflow tract which produced an elongated area of outflow narrowing. Fig 12 is an illustration of this type of obstruction. The maximal area of narrowing is present at the tips of the vertical arrows.

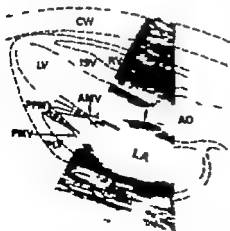


Fig 12 Long axis cross-sectional echocardiogram from a patient with discrete subvalvular aortic stenosis produced by a more diffuse area of fibro-muscular narrowing of the outflow tract. The more generalized area of narrowing is characterized by extensive inward curving of the linear echoes from the walls of the outflow tract with resultant narrowing of the vascular lumen in this region. The area of maximal obstruction is indicated by the vertical arrows (From Heyman AE et al Localization of left ventricular outflow obstruction by cross-sectional echocardiography *Am J Med* 60 38 1976)

detection of valvular aortic stenosis in patients with both calcific and congenitally stenotic aortic valves. They further suggest that the cross sectional systems offer at least a semi quantitative method for determining the severity of stenosis.

#### D Discrete Subvalvular Aortic Stenosis

Patients with discrete subvalvular aortic stenosis have conventionally been divided into two pathologic subgroups (23). In the first group the obstruction is produced by a thin discrete subvalvular membrane which may occur as an isolated lesion or may be superimposed on an area of fibromuscular narrowing of the outflow tract. The second is characterized by a diffuse fibromuscular ring which constricts a more extensive portion of the subvalvular region. This differentiation is clinically important since the extent of surgical revision and response to surgical repair differs markedly in these two groups of patients. To date we have had the opportunity to examine the

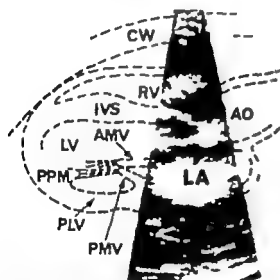


Fig 10 Long axis cross-sectional echogram from a child with discrete subvalvular aortic stenosis produced by a thin fibrous obstructing membrane located immediately beneath the aortic valve. There are two linear echoes within the mid portion of the outflow tract produced by the blood tissue interface at the inner margins of the subvalvular membrane (horizontal arrow). The membrane itself which lies between these echoes and the walls of the vessel is oriented parallel to the interrogating beam and therefore not visualized. (From Heyman AE et al Localization of left ventricular outflow obstruction by cross-sectional echocardiography *Amer J Med* 60 33 1976)



Fig 11 Long axis cross-sectional echogram recorded post operatively from a child with type I (membranous) subvalvular obstruction. The two linear echoes produced by the membrane are no longer present however there is a small residual echo producing ridge lying along the posterior margin of the outflow tract between the aortic root and anterior mitral leaflet. The small area of residual narrowing is indicated by the vertical arrow. (From Heyman AE et al Cross-sectional echocardiography in evaluating patients with discrete subaortic stenosis *Amer J Cardiol* 37 358 1976)

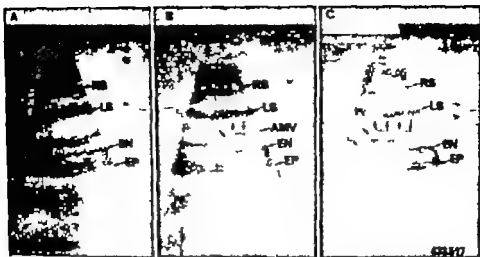


Fig 14: Serial long axis cross-sectional studies of the left ventricle at the level of the free edge of the mitral valve from a patient with IESS. Panel A is recorded 11 seconds after the R wave of the electrocardiogram and illustrates the normal systolic coaptation of the anterior and posterior mitral leaflets prior to the onset of systolic anterior motion. Panel B is recorded 6.04 seconds later illustrates the initiation of systolic anterior motion (vertical arrows). This systolic anterior motion begins at the point of coaptation of the anterior and posterior leaflets and spreads initially superiorly toward the interventricular septum. In Panel C recorded two hundredths of a second later the systolic anterior motion has extended further anteriorly and distally toward the papillary muscles (vertical arrows). In the subsequent frame the leaflet has moved fully up against the interventricular septum and can no longer be clearly distinguished from the septal slopes.

location of the systolic anterior motion relative to the closure point of the anterior mitral leaflet and the manner in which this obstruction develops. Systolic anterior motion begins at the junction of the anterior and posterior mitral leaflets and spreads anteriorly toward the interventricular septum and distally toward the papillary muscles. Henry et al (27) in a combined cross sectional and M-mode study showed a relationship between the distance of the anterior mitral leaflet from the interventricular septum and the occurrence of obstruction. They further demonstrated that the abnormal anterior mitral leaflet motion occurred in the plane perpendicular to the pull of the papillary muscles suggesting that the papillary muscles did not draw the anterior leaflet up against the enlarged septum as had been previously suggested. They concluded based on these observations that the phenomenon of systolic anterior motion or functional obstruction was produced by a Venturi effect caused by the acceleration of blood through the narrowed outflow space between the mitral leaflet and the interventricular septum and hypothesized that the creation of obstruction was dependent upon a critical distance between these two structures for any given rate of ejection. Thus while the studies have to date not expanded our diagnostic ability

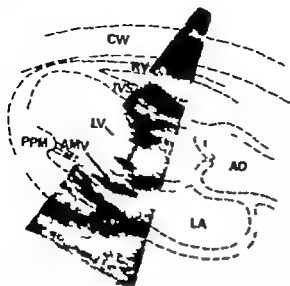


Fig 13 Long axis cross-sectional echocardiogram of the left ventricular outflow tract from a patient with a variant of discrete subaortic aortic stenosis. In this patient there is a marked increase in septal thickness at the basal portion of the interventricular septum producing an area of shelf like narrowing of the outflow tract. There is corresponding systolic anterior motion of the mid portion of the mitral valve. The maximal area of obstruction is indicated by the vertical arrow. (From Weyman AE et al. Localization of outflow obstruction by cross-sectional echocardiography. *Am J Med* 60:33, 1976)

tion by cross-sectional echocardiography. *Am J Med* 60:33, 1976)

The final type of outflow obstruction was observed to occur at a slightly lower level of the outflow tract. In this case there was a localized area of marked increase in septal thickness occurring at the basal margin of the interventricular septum and producing an area of shelf like obstruction extending downward into the outflow tract. There was a corresponding fixed echo extending anteriorly from the mid portion of the anterior mitral leaflet (fig 13). During systole there was dynamic anterior motion of this localized protrusion of the anterior mitral leaflet toward the downward projection from the interventricular septum. The remainder of the septum was of normal thickness as was the posterior wall. The septal posterior wall ratio at the level of the free edge of the mitral valve therefore was normal.

### E Idiopathic Hypertrophic Subaortic Stenosis

M-mode echocardiography has been a sensitive method for diagnosing idiopathic hypertrophic subaortic stenosis (6,7). The resolution and sampling rate of this system permits the thickness of the interventricular septum to be accurately determined and the abnormal motion patterns of the anterior mitral leaflet clearly recorded. In addition to permitting the diagnosis of IHSS, the M-mode system has allowed the underlying genetic marker, asymmetric septal hypertrophy (ASH), to be defined (11,26) and the hereditary pattern of this lesion to be delineated (10). In addition, some estimate of the severity of obstruction can be determined (8). While probably not significantly adding to our ability to diagnose IHSS, the cross-sectional system permits the location and nature of the obstructing lesion to be more clearly defined. Several authors have examined the pattern of anterior mitral leaflet motion in patients with IHSS using different cross-sectional systems and confirmed the location within the ventricle (27,28) and pattern of development of the obstructing lesion. Fig 14 is a series of three recordings demonstrating the

- 3 JAMES R H BERRY C L and ABERDEEN E Congenital bicuspid aortic valves associated with coarctation of the aorta in children  
Brit Heart J 31 127 1969
- 4 FEIGENBAUM H Echocardiography Second Edition Lea & Febiger Philadelphia 1976
- 5 GRAMIAK R and Wang R Cardiac Ultrasound The W B Mosby Co St Louis 1975
- 6 SHAH P M GRAMIAK R and KRAMER D H Ultrasound localization of left ventricular outflow obstruction in hypertrophic obstructive cardiomyopathy Circulation 40 3 1969
- 7 SHAH P M GRAMIAK R ADELMAN A G and WIGLE E D Role of echocardiography in diagnostic and hemodynamic assessment of hypertrophic subaortic stenosis Circulation 44 891 1971
- 8 HENRY W L CLARK C E GLANCY D L and EPSTEIN S E Echocardiographic measurement of the left ventricular outflow gradient in idiopathic hypertrophic subaortic stenosis New Engl J Med 288 989 1973
- 9 POPP R L and HARRISON D C Ultrasound in the diagnosis and evaluation of therapy of idiopathic hypertrophic subaortic stenosis Circulation 40 905 1969
- 10 CLARK C E HENRY W L and EPSTEIN S E Familial prevalence and genetic transmission of idiopathic hypertrophic subaortic stenosis New Engl J Med 289 709 1973
- 11 HENRY W L CLARK C E AND EPSTEIN S E Asymmetric septal hypertrophy The unifying link in the IHSS disease spectrum Observations regarding its pathogenesis pathophysiology and course Circulation 47 827 1973
- 12 GRAMIAK R and SHAH P M Echocardiography of the normal and diseased aortic valve Radiology 96 1 1970
- 13 FEIZI M SYMONS C YACOB M Echocardiography of the aortic valve II Studies of normal aortic valve aortic stenosis aortic regurgitation and mixed valve disease Brit Heart J 36 341 1974
- 14 YEH H C WINSBERG F MERCER E M Echocardiographic aortic valve orifice dimension Its use in evaluating aortic stenosis and cardiac output J Clin Ultrasound 1 182 1973
- 15 GOLDBERG B B Suprasternal ultrasonography JAMA 215 245 1971
- 16 GOLDBERG B B Ultrasonic measurement of the aortic arch right pulmonary artery and left atrium Radiology 101 383 1971
- 17 ALLEN H D GOLDBERG S J Usefulness of biaxial left atrial dimension measurements by echocardiography (abstr) Ultrasound 2 222 1974
- 18 KEYMAN A E CALDWELL R L HUPWITZ R A GIBBO D A DILLON J C FEIGENBAUM H and GREEN D Cross-sectional echocardiographic detection of aortic obstruction II Coarctation of the aorta Circulation (submitted for publication)



IHSS they do permit a relatively clear visualization of the pattern of obstruction and its development. In this way the cross sectional system should help in understanding the pathophysiology of this phenomenon.

### CONCLUSION

As suggested in this report cross-sectional echocardiography is a valuable method for visualizing areas of obstruction at all levels in the left ventricular outflow tract. It is particularly useful for defining regional changes in vascular size in a tubular structure such as the aorta. By permitting visualization of the aorta both proximal and distal to the area of obstruction it allows the characteristic change in luminal diameter to be more fully appreciated. At the valvular level the cross-sectional technique permits the full geometric configuration of the domed stenotic valve to be visualized thereby allowing the stenotic valve itself to be detected and the severity of the obstructing lesion estimated. In areas of functional obstruction the cross sectional system allows the pattern of development of the obstruction to be more fully visualized and hence the pathophysiologic mechanisms producing this obstruction examined. In addition to defining individual areas of outflow obstruction the ability to quickly examine the entire length of the left ventricular outflow tract should permit presence of multiple lesions to be detected. The cross sectional technique should therefore be an important tool in the armamentarium of those interested in detecting and defining the morphologic and functional characteristics of lesions producing left ventricular outflow obstruction.

### ACKNOWLEDGEMENT

*This work was supported in part by the Herman C. Exner Fund and by Grants HL-06308, HL-05363 and HL-07182 from the National Heart, Lung and Blood Institute of the National Institutes of Health, U.S. Public Health Service and the American Heart Association, Indiana Affiliate.*

### REFERENCES

1. PERLOFF, J. K. The clinical recognition of congenital heart disease. Philadelphia: W. B. Saunders Co. 1970. p. 100.
2. EDWARDS, J. E. and CAREY, L. S., NEUFELD, H. M. and LESTER, R. G. Congenital heart disease. Philadelphia: W. B. Saunders Co. 1965. p. 365.

3. TAKES R H BERRY C L and ABERDEEN E Congenital bicuspid aortic valves associated with coarctation of the aorta in children  
Brit Heart J 31 127 1969
4. FEIGENBAUM H Echocardiography Second Edition Lea & Febiger  
Philadelphia 1976
5. GRAMIAK R and Waag R Cardiac Ultrasound The C V Mosby Co  
St Louis 1975
6. SHAH P M, GRAMIAK R and KRAMER D H Ultrasound localization of left ventricular outflow obstruction in hypertrophic obstructive cardiomyopathy Circulation 40 3 1969
7. SHAH P M GRAMIAK R, ADELMAN A G and WIGLE E D Role of echocardiography in diagnostic and hemodynamic assessment of hypertrophic subaortic stenosis Circulation 44 891 1971
8. HENRY W L CLARK C E GLANCY D L and EPSTEIN S E Echocardiographic measurement of the left ventricular outflow gradient in idiopathic hypertrophic subaortic stenosis New Engl J Med 288 989 1973
9. POPP R L and HARRISON D C Ultrasound in the diagnosis and evaluation of therapy of idiopathic hypertrophic subaortic stenosis Circulation 40 905 1969
10. CLARK C E HENRY W L and EPSTEIN S E Familial prevalence and genetic transmission of idiopathic hypertrophic subaortic stenosis New Engl J Med 289 709 1973
11. HENRY W L CLARK C E AND EPSTEIN S E Asymmetric septal hypertrophy The unifying link in the IHSS disease spectrum Observations regarding its pathogenesis pathophysiology and course Circulation 47 827 1973
12. GRAMIAK R. and SHAH P M Echocardiography of the normal and diseased aortic valve Radiology 96 1 1970
13. FEIZI O SYMONS C YACCOUB M Echocardiography of the aortic valve Studies of normal aortic valve aortic stenosis aortic regurgitation and mixed valve disease Brit Heart J 36 341 1974
14. YEH H C WINKSBERG F MERCER E M Echocardiographic aortic valve orifice dimension its use in evaluating aortic stenosis and cardiac output J Clin Ultrasound 1 182 1973
15. GOLDBERG B B Suprasternal ultrasonography JAMA 215 245 1971
16. GOLDBERG B B Ultrasonic measurement of the aortic arch right pulmonary artery and left atrium Radiology 101 383 1971
17. ALLEN H H GOLDBERG S J Usefulness of biaxial left atrial dimension measurements by echocardiography (abstr) Ultrasound 2 222 1974
18. WETZEL A E CALDWELL R L HURWITZ R A GIROD D A DILLON J C FEIGENBAUM H and GREEN D Cross sectional echocardiographic detection of aortic obstruction II Coarctation of the aorta Circulation (submitted for publication)

- 19 PETERSON T A TODD D B EDWARDS J E Supravalvular aortic stenosis *J Thorac Cardiovasc Surg* 50 734 1968
- 20 MANDA H C , GRAMIAK R MANNING, J MAHONEY E B LIBCHIK E O DEWEESE J A Echocardiographic recognition of the congenital bicuspid aortic valve *Circulation* 49 870 1974
- 21 WEYMAN A E FEIGENBAUM H DILLON J C and CHANG S Cross sectional echocardiography in assessing the severity of valvular aortic stenosis *Circulation* 52 828 1975
- 22 WEYMAN A E FEIGENBAUM H HURWITZ R A GIROD D A and DILLON J C Cross-sectional echocardiographic assessment of the severity of aortic stenosis in children *Circulation* 55 773 1977
- 23 KELLY D T WULFSBERG E ROWE, R D Discrete subaortic stenosis *Circulation* 46 309 1972
- 24 WEYMAN A E FEIGENBAUM H HURWITZ R A GIROD D A DILLON J C and CHANG S Cross sectional echocardiography in the evaluation of patients with discrete subaortic stenosis *Amer J Cardiol* 37 358 1976
- 25 WEYMAN A E FEIGENBAUM H HURWITZ R A GIROD D A DILLON J C and CHANG S Localization of left ventricular outflow obstruction by cross sectional echocardiography *Amer J Med* 60 33 36 1976
- 26 HENRY W L , CLARK C E and EPSTEIN S E Asymmetric septal hypertrophy The unifying link in the IHSS disease spectrum Observations regarding its pathophysiology and course *Circulation* 47 827 1973
- 27 HENRY W L CLARK C E GRIFFITH J M and EPSTEIN S E Mechanism of left ventricular outflow obstruction in patients with obstructive asymmetric septal hypertrophy (idiopathic hypertrophic subaortic stenosis) *Amer J Card* 35 337 1975
- 28 MARTIN R P FRENCH J W PITTMAN M M and POPP R L Analysis of idiopathic hypertrophic subaortic stenosis by wide angle phased array echocardiography *Circulation* 53 11 191 1976

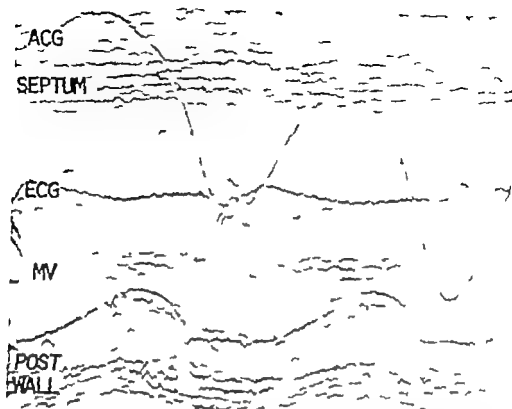
## THE USE OF M-MODE ECHOCARDIOGRAPHY IN ISCHAEMIC HEART DISEASE

D G GIBSON

*From Brompton Hospital London SW3 6HP*

The characteristic feature of left ventricular involvement in ischaemic heart disease is its regional distribution due to the non-uniform nature of the coronary artery lesions. This results in a number of disturbances of function of which the best recognized are a regional reduction in wall movement during systole, aneurysm formation popularly supposed to be accompanied by paradoxical movement and finally a generalized reduction in wall movement accompanied by an increase in cavity size so-called ischaemic cardiomyopathy. These abnormalities all have in common a disturbance in the overall amplitude or direction of wall movement and their analysis in individual patients is usually based merely on inspection of angiograms. Another type of interference with the action of the left ventricle may occur in ischaemic heart disease however in which the overall amplitude and direction of wall movement are both normal but in which its timing is disturbed. This is much harder to characterize by direct inspection of the angiogram and yet may have effects on left ventricular function out of all proportion to the extent of myocardium involved by causing incoordinate contraction. M-mode echocardiography allows left ventricular endocardium to be unequivocally identified throughout the cardiac cycle and its movement recorded with a frequency response considerably superior to that of current angiographic techniques so that it is an excellent method for the analysis of these disturbances.

In figure 1 is shown the echocardiogram of a patient who developed a low output state after cardiac surgery. It will be seen that though the amplitude of septal movement is reduced as is frequently the case after open heart surgery that of posterior wall movement is normal. However it is apparent from the mitral valve echo that virtually all the increase in transverse diameter that occurs does so before the onset of mitral valve opening and therefore before the onset of filling. This increase in left ventricular dimension thus represents no more than a change in cavity shape during the period of isovolumic relaxation and as such likely to have contributed to poor overall left ventricular performance. Wall movement in this



*Fig 1 Echocardiogram showing left ventricular cavity and mitral valve echoes from a patient who developed a low cardiac output after surgery. Mitral valve opening is delayed with respect to wall movement*

patient is abnormal not in terms of its magnitude or direction but in its timing and it has been detected by considering the dimension not in isolation but by correlating it with events referable to the function of the cavity as a whole here the start of filling. This method has proved a sensitive one and abnormalities of isovolumic relaxation have been detected in patients with coronary artery disease where they correlate closely with the presence of regional reduction in wall movement seen on angiography (3)

The onset of mitral valve opening is only one of several ways in which the timing of overall left ventricular function can be assessed. A more versatile one is to use the left ventricular pressure trace to construct pressure-dimension loops. The normal pressure-dimension loop is approximately rectangular (Fig 2) with little change in dimension during the upstroke and downstroke of the pressure trace which approximate in timing to the periods of isovolumic contraction and relaxation. Conversely during ejection and filling changes in pressure are small. The rectangular configuration of the loop has functional significance in that the area of the loop represents the actual work done per unit area on the circulation by myocardium in the region studied while the maximum work that could have been done by the myocardium operating over the same range of pressure and

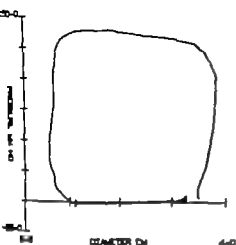


Fig 2 Pressure-dimension loop from a normal subject

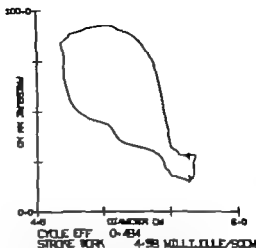


Fig 3 Pressure-dimension loop from a patient with ischaemic heart disease

dimension is given by the product of the two i.e. by the area of the rectangle that just encloses the loop. The ratio of loop area to that of the rectangle thus represents the efficiency of transfer of mechanical energy generated by the myocardium to the circulation. The pressure-dimension loop from a patient with ischaemic heart disease is shown in fig 3. It is apparent that the loop is distorted due mainly to dimension changes during the two isovolumic periods causing a drop in the efficiency of energy transfer to less than 50%. Pressure-dimension loops can thus be used to demonstrate incoordinate contraction and when abnormalities of this sort occur during the isovolumic periods they may have considerable functional significance.

Unfortunately measurement of left ventricular pressure requires cardiac catheterization. In order to detect abnormal wall movement however it is not the absolute value of pressure that is required but only the timing of the upstroke and the downstroke and these latter have been shown to be very close to the corresponding events on the apexcardiogram (2,5). We have therefore explored the use of loops constructed from left ventricular dimension and apexcardiogram which have proved to be rectangular in all of more than 50 normal subjects studied. In the presence of mitral regurgitation there is a reduction in dimension during the upstroke and of aortic regurgitation there is an increase in dimension during the downstroke as would be expected from the basic haemodynamic disturbances in these conditions. Many patients with ischaemic heart disease similar abnormal

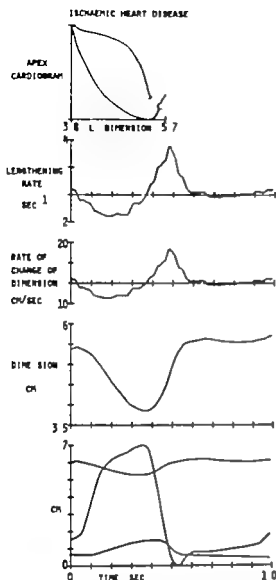


Fig 4 Apexcardiogram echo dimension loop from a patient with ischaemic heart disease. There is a reduction in dimension during the upstroke and an increase in dimension during the downstroke of the apexcardiogram.

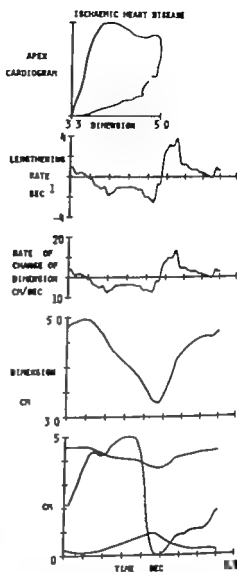


Fig 5 Apexcardiogram echo dimension loop from another patient with ischaemic heart disease. The abnormalities are the reverse of those shown in fig 4.

ties may also be found in the absence of valvular regurgitation examples being given in fig 4 and 5. In these circumstances a reduction in dimension during the upstroke of the apexcardiogram represents an abnormality of isovolumic contraction and during the downstroke one of early relaxation. Such abnormalities can also be detected by suitable analysis of angiograms (3) (Prewitt and Brown 1976). Using these methods angiograms and apexcardiogram-echo dimension relations were compared in 50 patients with ischaemic heart disease. In this study (Doran, Traill, Gibson and Brown unpublished) both specificity and sensitivity of the echo method were found to be greater

than 80 % with respect to the angiograms. The method has also been of value in detecting incoordinate contraction in patients with valvular heart disease or cardiomyopathy in the absence of coronary artery disease. It is useful in the follow-up of patients after saphenous by pass grafting when successful surgery may be followed by a return of the loop towards normal. Finally it can detect postoperative left ventricular disease after valve replacement and thus monitor the quality of myocardial preservation (4).

This approach clearly does not replace left ventricular angiography and coronary arteriography as a means of studying patients with ischaemic heart disease. However using traditional methods the nature of the complex physiological disturbance to left ventricular function may not be apparent from delineation of a series of anatomical abnormalities and it is in this field that the method appears to have value. It is non-invasive so that repeated observations can be made in individual patients and it can be performed in circumstances such as the postoperative ward where cardiac catheterization would not be possible. It is a simple way of detecting the presence of incoordinate contraction in patients with any type of heart disease and of following changes due to therapy or progression of underlying pathological processes.

#### REFERENCES

1. UPTON M T, GIBSON D G and BROWN D J. Echocardiographic assessment of abnormal left ventricular relaxation in man. *Brit Heart J* 38 1001 1976
2. GIBSON D G. and BROWN D J. Assessment of left ventricular systolic function from simultaneous left ventricular echocardiographic and pressure measurements. *Brit Heart J* 38 8 1976
3. MAXOLAS J, RUTISHAUSER W and WIRZ P. Time relation between apexcardiogram and left ventricular events using simultaneous high fidelity tracings in man. *Brit Heart J* 37 1263 1975
4. YENCO A, GIBSON D G and BROWN D J. Relation between apexcardiograms and changes in left ventricular pressure and dimension. *Brit Heart J* 39 117 1977
5. GIBSON D G, PREWITT T A. and BROWN D J. Analysis of left ventricular wall movement during isovolumic relaxation and its relation to coronary artery disease. *Brit Heart J* 38 1010 1976



# EFFECT OF INCREASES IN AFTERLOAD ON THE SYSTOLIC THICKENING OF ACUTELY ISCHEMIC MYOCARDIUM AN EXPERIMENTAL ECHOCARDIOGRAPHIC STUDY

R E KERBER M E MARCUS J EHRHARDT AND F M ABOUD

*From the Cardiovascular Center and The Cardiovascular Division, Department of Internal Medicine and Department of Radiology, University of Iowa Hospitals, Iowa City, Iowa*

## ABSTRACT

Changes in arterial blood pressure have been shown to alter epicardial ST segment elevations and have been advocated to minimize infarct size and salvage ischemic myocardium. The effect of such changes on the regional function of ischemic myocardium has not been established. To investigate this we studied the effect of increased afterload on the systolic wall thickening and myocardial perfusion of ischemic ventricular myocardium. In 20 open-chest dogs an echocardiographic transducer was fixed to the exposed right ventricle and directed to record the motion of the left ventricular posterior wall. Posterior ischemia was created by occlusion of the circumflex coronary so that the ultrasound beam registered the motion of acutely ischemic myocardium. The ratio of end-systolic to end-diastolic posterior wall thickness (PTs/PTd) was greater than 1 (i.e. systolic thickening) before and less than 1 (systolic thinning) after posterior ischemia. Mean arterial pressure was then increased by infusion of methoxamine (MX) or norepinephrine (NE) or by aortic constriction (CN). PTs/PTd improved from  $0.89 \pm 0.03$  to  $1.10 \pm 0.06$  ( $p < 0.05$ ) with CN. Perfusion of the ischemic areas assessed with  $8\mu$  radioactive labeled microspheres showed a corresponding improvement; with MX ischemic myocardial perfusion improved from  $32.4 \pm 6.2$  to  $59.6 \pm 13.8$  ml/100g/min ( $p < 0.05$ ) and with CN perfusion rose from  $30.2 \pm 9.3$  to  $43.8 \pm 10.3$  ml/100g/min ( $p < 0.05$ ). Thus increase in afterload improved both the perfusion and regional function of acutely ischemic myocardium.

Changes of arterial blood pressure have been shown to alter epicardial ST segment elevations in dogs subjected to acute coronary occlusion. Such changes may be useful in patients with acute myocardial infarction to "salvage jeopardized myocardium" (1). The effect of such arterial pressure changes on the regional function of acutely ischemic myocardium has not been established.

The purpose of this study was to assess the effect of increases in afterload on the function of acutely ischemic myocardium and to correlate the observed changes with regional myocardial perfusion. We also wished to compare the effects of different methods of increasing afterload and therefore studied 3 agents: norepinephrine, a vasoconstrictor with positive inotropic effects and direct effects on coronary vessels; methoxamine, a vasoconstrictor with beta adrenergic blocking properties which also has direct effects on coronary vessels and aortic constriction which has no direct inotropic or coronary vasoactive effects. An echocardiographic technique was used to measure dynamic changes in left ventricular wall thickness, a recently emphasized parameter of regional myocardial function in the presence of ischemia (2).

#### METHODS

Twenty adult mongrel dogs weighing 16 to 23 kg were anaesthetized with chloralose-urethane IV. An endotracheal tube was placed and the dogs were ventilated using Harvard respirator, room air and supplemental oxygen. Arterial  $PO_2$  and pH were monitored frequently and were maintained in a physiologic range using adjustments of tidal volume. Via a midsternal thoracotomy and pericardiotomy the heart was exposed and suspended in a pericardial sling. The circumflex coronary artery or posterior descending coronary artery was dissected free and a snare ligature placed around it. Heparin (250 units/kg IV) was given and # 8 French polyurethane catheters were inserted retrograde into the left ventricle and aortic root for pressure monitoring using Statham P23 strain gauges at midchest level. An electrocardiogram was also displayed. Recordings were made utilizing an Electronics for Medicine CR 12 multichannel photographic recorder.

#### REGIONAL MYOCARDIAL FUNCTION

Echocardiographic recordings of the interventricular septum, left ventricular

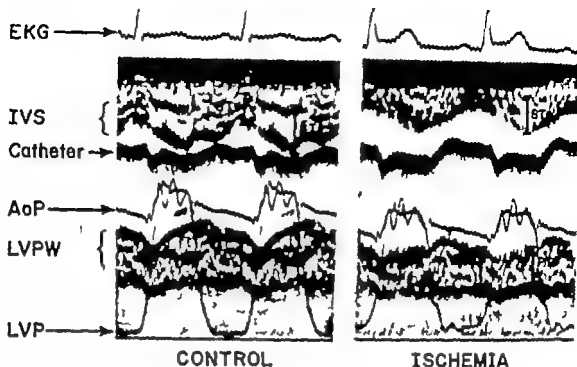


Fig 1 Illustrative echocardiographic recordings before ("control") and 20 minutes after ("ischemia") posterior coronary occlusion. The vertical bars indicate end-diastolic and end-systolic septal and posterior wall thickness. End-systolic septal thickness was taken at the point at which the septum was thickest. With posterior ischemia abolition of normal posterior wall thickening occurred while septal thickening was preserved. Abbreviations: EKG = electrocardiogram, IVS = interventricular septum, AoP = aortic pressure, LVPW = left ventricular posterior wall, LVP = left ventricular pressure, Std = septal thickness end-diastolic, Std = septal thickness end-systolic, Ptd = posterior wall thickness end-diastolic, Pte = posterior wall thickness end-systolic.

cavity and left ventricular posterior wall were obtained using a method which has previously been described in detail (3). Briefly, a 2.25 MHz 5 cm focussed transducer was placed on the exposed anterior right ventricular surface and directed inferiorly to the mitral leaflet echoes to record the left ventricular posterior wall motion. Thus, after circumflex coronary occlusion, the ultrasound beam was reflected from and registered the motion of acutely ischemic posterior myocardium (4,5). The transducer was fixed to a rigid bar to minimize transmitted motion from the heart and to provide a fixed reference point.

To verify structure identification, we injected 5 ml of normal saline through a catheter in the left atrium. This produces ultrasonic contrast reflections which fill the chamber and outline the endocardial-blood interfaces (6). The sensitivity of the ultrasonoscope was manipulated to best define the epicardial and endocardial echoes. The thickness of the septum and posterior wall was measured at end-diastole and end-systole.

The exact points of measurement are shown in Fig 1. The ratio of end systolic septal thickness (STs) to end-diastolic septal thickness (STd) was expressed as a simple ratio (STs/STd). A similar expression was used for the posterior wall thickness (PTs/PTd).

#### MYOCARDIAL PERFUSION

Left ventricular myocardial perfusion was determined using 7-10  $\mu$  micro spheres labeled with  $^{141}\text{Ce}$ ,  $^{85}\text{Sr}$ ,  $^{67}\text{Cr}$  and  $^{46}\text{Sc}$ . For each perfusion measurement the vial containing the microspheres and one drop of Tween-80 was agitated mechanically for at least 3 minutes to achieve adequate dispersal of the spheres. The microspheres were suspended in saline and injected over a 5 second period into the left atrium. Left atrial catheter was then flushed with 5 ml of saline. Beginning one minute before injection and continuing for 3 minutes after injection, blood for reference flow determinations was withdrawn from the right brachial and femoral arteries simultaneously at 2.06 ml/min.

After the echocardiographic recordings were completed two metal probes were positioned along the ultrasound transducer and passed through the heart in parallel to mark the path of the ultrasound beam. To minimize deformation of the left ventricular wall (and consequent errors in beam localization) we placed sharp #20 needles through the beating heart. The points of intersection of the probes with the left ventricular posterior endocardium were noted to verify that the specific myocardial segments traversed by the ultrasound beam were hypoperfused segments from the area supplied by the ligated coronary artery. The animals were then killed with an injection of potassium chloride.

The heart was excised and the free walls of the right ventricle, the right and left atrium, great vessels, valves, surface vessels and epicardial fat were removed. Utilizing the posterior descending coronary as a reference point, the left ventricle was divided into four equal levels of eight segments each, and each segment was divided into three layers: endocardium, mid-wall and epicardium. Thus the left ventricle was divided into 96 segments of about 1.6 x 1.6 x 0.3 cm in size, with an average weight of 0.8 g. The relative geometric position of each segment was constant from animal to animal.

Using techniques previously described in detail (7) we determined the perfusion of each of the 96 small myocardial segments as well as the size of the ischemic area and the endocardium-epicardium perfusion ratio. Ischemic

segments were identified utilizing a statistical method (7) which in effect estimates the heterogeneity of perfusion to normally perfused segments and then uses this information to establish the level below which perfusion of normal segments does not fall. Segments found to have such abnormally low perfusion (seen only following coronary ligation) were classified as ischemic.

## EXPERIMENTAL PROTOCOL

Prior to the coronary occlusion, control hemodynamic and echocardiographic recordings were obtained and an injection of microspheres made. The previously placed circumflex or posterior descending ligature was then tightened to occlude the artery. The animals were allowed to stabilize for 20 minutes after which a second set of hemodynamic and echocardiographic recordings were made and another injection of microspheres with a different label was made. Hereafter, the animals were divided into three groups. Group I animals ( $n = 7$ ) received norepinephrine 0.7 to 15.0  $\mu\text{g}/\text{min}$  IV in order to raise mean aortic pressure to approximately 120% and then 140% of the level at the initial postcoronary occlusion recording. Group II animals ( $n = 8$ ) received methoxamine 0.10 to 1.2  $\text{mg}/\text{min}$  IV to similar end points. In group III dogs ( $n = 5$ ) an umbilical tape was placed around the descending aorta and this was tightened to two different levels of aortic constriction. In each case the increase in pressure was maintained for at least 5 minutes while echocardiographic and hemodynamic recordings were obtained, microspheres injected and reference blood withdrawal accomplished. Standard statistical methods were used for analysis. All data are expressed as mean  $\pm$  standard error of the mean.

## RESULTS

Hemodynamic data The hemodynamic data are summarized in table 1. The control mean aortic pressures were higher in the group of dogs which were to receive methoxamine after coronary occlusion. The reason for this is not clear. Despite our attempts to achieve comparable end points, methoxamine also effected a greater relative rise in mean aortic pressure than did norepinephrine. Aortic constriction produced a smaller rise in aortic mean pressure than did the two drugs since this intervention produced primarily systolic hypertension with a relatively modest rise in diastolic pressure.

Myocardial function The echocardiographic wall thickening data are summarized in table 1 and in fig 2, 3, 4. The ratio  $\text{PTs}/\text{PTd}$  was 1.0 or greater ( $\equiv$  systolic thickening) in all of the 20 control recordings and less

Table 1

## A. Animals receiving methoxamine after coronary occlusion (n=5)

	Control Mean±SD	Coronary Occlusion Mean±SD	Intervention Mean±SD	Intervention 2nd level Mean±SD
Heart rate beats/min	140±5	129±9	128±8	124±7
Aortic systolic pressure mmHg	144±10	124±10	137±11	133±13*
Aortic mean pressure mmHg	120±10	110±11	123±11	124±14*
Aortic diastolic pressure mmHg	123±10	104±11	126±11	125±14*
LV end-diastolic pressure mmHg	8±1	14±1	14±2	19±2
PTs/PTd	1.24±0.07	0.80±0.03	1.01±0.04	1.19±0.06*
STs/STd	1.20±0.07	1.27±0.13	1.27±0.06	1.24±0.07
Perfusion ischaemic segments ml/100g/min	87.2±13.8	22.6±3.2	68.9±17.3	88.0±13.8*
End-EPI ratio ischaemic segments	1.2±0.1	0.7±0.1	0.8±0.1	0.8±0.1
Perfusion nonischaemic segments ml/100g/min	88.9±11.9	73.7±9.8	77.9±10.8	103.9±11.9*
End-EPI ratio nonischaemic segments	1.2±0.1	1.2±0.0	1.2±0.1	1.2±0.1

## B. Animals receiving norepinephrine after coronary occlusion (n=7)

Heart rate, beats/min	140±9	127±9	135±4	144±8*
Aortic systolic pressure mmHg	140±4	87±4	71±9*	144±5*
Aortic mean pressure mmHg	89±4	89±4	70±9*	134±5*
Aortic diastolic pressure mmHg	89±4	72±4	82±9*	123±5
LV end-diastolic pressure mmHg	22±3	13±3	13±3	14±3
PTs/PTd	1.12±0.06	0.80±0.03	0.70±0.07*	0.97±0.07*
STs/STd	1.12±0.01	1.43±0.10	1.28±0.09*	1.34±0.07
Perfusion ischaemic segments ml/100g/min	79.9±5.1	23.7±4.6*	31.9±5.4*	67.1±5.2*
End-EPI ratio ischaemic segments	1.1±0.1	0.7±0.1	0.7±0.1	0.7±0.1
Perfusion nonischaemic segments	71.6±7.1	70.8±9.5	68.3±1.4	124.1±5.8*
End-EPI ratio nonischaemic segments	1.2±0.1	1.1±0.0	1.1±0.0	1.1±0.1

## C. Animals undergoing aortic constriction after coronary occlusion (n=7)

Heart rate, beats/min	170±22	170±21	170±21	170±24
Aortic systolic pressure mmHg	170±22	170±21	170±20*	162±13*
Aortic mean pressure mmHg	104±13	100±13	114±12*	120±12*
Aortic diastolic pressure mmHg	57±13	66±15	90±17	100±11
LV end-diastolic pressure mmHg	12±3	11±3	14±3	20±2*
PTs/PTd	1.27±0.02	0.87±0.03	0.57±0.04*	0.94±0.03
STs/STd	1.25±0.10	1.90±0.10	1.10±0.06	1.27±0.06
Perfusion ischaemic segments ml/100g/min	88.3±13.1	26.2±3.3	28.3±7.2	43.8±10.2*
End-EPI ratio ischaemic segments	1.1±0.0	0.8±0.2	0.8±0.2	0.8±0.2
Perfusion nonischaemic segments ml/100g/min	86.6±17.4	86.7±13.8	61.4±12.2	122.8±10.2*
End-EPI ratio nonischaemic segments	1.1±0.0	1.1±0.0	1.0±0.1	1.1±0.0

Abbreviations: p, p.OE control vs coronary occlusion

p, p.OE intervention vs. coronary occlusion

LV left ventricle, End-EPI endocardial-myocardial Per PTs/PTd and STs/STd see text.

then 1 (systolic thinning) in 17 of the 20 dogs after posterior ischemia (In the three remaining animals the ratio fell to 1.0) Mean PTs/PTd increased with methoxamine (Fig 2) with norepinephrine (Fig 3) and with aortic constriction (Fig 4). Considering the effects of these maneuvers on nonischemic myocardium (the interventricular septum) STs/STd of all the dogs exceeded 1.0 control (i.e. systolic septal thickening). After posterior coronary occlusion STs/STd of the whole group increased from 1.27±0.04 to 1.37±0.07 (p<0.05). With each subsequent intervention STs/STd fell slightly but never to 1.0.

### METHOXAMINE

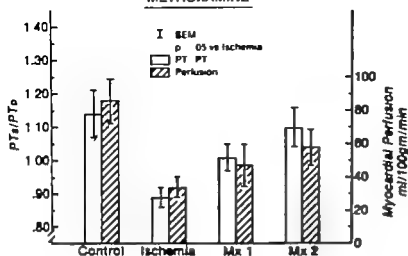


Fig 2 Effect of methoxamine on ischemic posterior wall thickening and perfusion SEM - standard error of the mean Mx = methoxamine

### NOREPINEPHRINE

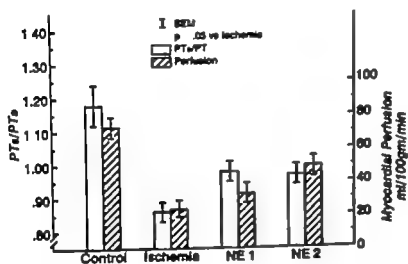


Fig 3 Effect of norepinephrine on ischemic posterior wall thickening and perfusion NE = norepinephrine

### AORTIC CONSTRICTION

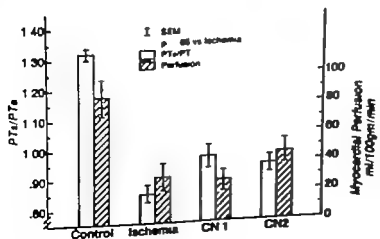


Fig 4 Effect of aortic constriction on ischemic posterior wall thickening and perfusion CN = aortic constriction

Myocardial Perfusion The microsphere derived perfusion data are summarized in Table 1 and Fig 2 3 4. With methoxamine perfusion of the ischemic areas improved from  $32.4 \pm 6.2$  to a maximum of  $59.6 \pm 13.8$  ml/100 g/min ( $p < 0.05$ ) (Fig 2). With norepinephrine perfusion increased from  $23.1 \pm 4.6$  to  $47.1 \pm 6.2$  ml/100 g/min ( $p < 0.05$ ) (Fig 3). With aortic constriction the perfusion increased from  $30.2 \pm 9.3$  to  $43.2 \pm 10.3$  ml/100 g/min ( $p < 0.05$ ) (Fig 4). Perfusion of the nonischemic areas rose (Table 1) with each intervention. The endocardial-epicardial perfusion ratios were greater than one in control determinations and less than one in the ischemic areas after coronary occlusion. With the interventions the endo-epi ratios did not change significantly (Table 1).

### DISCUSSION

In this study we used systolic thickening or thinning assessed echocardiographically to assess the function of acutely ischemic myocardium. PTs/PTd appears to be influenced strongly by the perfusion of the area of myocardium sampled by the ultrasound beam, since wall thickening was seen in normally perfused areas and wall thinning was associated with the severe hypoperfusion of the ischemic areas.

Decreases in afterload accomplished with any of the three interventions we used had beneficial effects on the thinning of acutely ischemic myocardium. Thinning was virtually abolished with norepinephrine and aortic constriction (PTs/PTd approached 1.0) and with methoxamine thickening of the initially ischemic wall occurred. These changes probably reflected improvement in the perfusion of the areas supplied by the occluded coronary artery; although perfusion of these areas was not restored to pre-occlusion levels significant increases in perfusion did occur with each intervention. Norepinephrine has positive inotropic effects and the improvement in PTs/PTd could be due to these. However similar improvement occurred with methoxamine and aortic constriction which lack positive inotropic effects. This again suggests that the change in thickening was primarily due to improved perfusion. The reason for the increase in flow to the ischemic areas is not determined by this study. It may be due to increased collateral flow. Or since the perfusion distribution after coronary occlusion is spatially and temporally heterogeneous it may primarily reflect improved perfusion to normally perfused areas lying within the ischemic zone. A mixture of both these mechanisms is also possible.

Perfusion of the nonischemic areas also rose with the pressor interventions but unlike the ischemic posterior wall this was accompanied by small declines



### METHOXAMINE

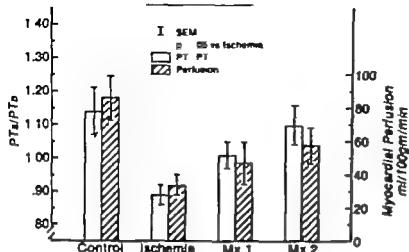


Fig 2 Effect of methoxamine on ischemic posterior wall thickening and perfusion SEM = standard error of the mean MI = methoxamine

### NOREPINEPHRINE

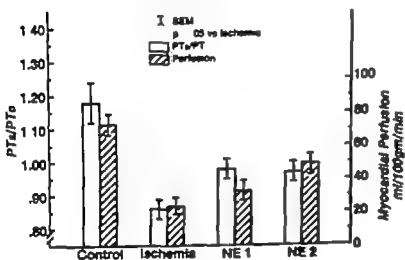


Fig 3 Effect of norepinephrine on ischemic posterior wall thickening and perfusion NE = norepinephrine

### AORTIC CONSTRICTION

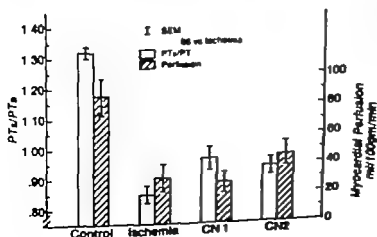


Fig 4 Effect of aortic constriction on ischemic posterior wall thickening and perfusion CN = aortic constriction

radial Perfusion The microsphere derived perfusion data are summarized in Table 1 and Fig 2, 3, 4. With methoxamine perfusion of the ischemic areas increased from  $32.4 \pm 6.2$  to a maximum of  $59.6 \pm 13.8$  ml/100 g/min ( $p < 0.05$ ) (Fig 2) norepinephrine perfusion increased from  $23.1 \pm 4.6$  to  $47.1 \pm 6.2$  ml/100 g/min ( $p < 0.05$ ) (Fig 3). With aortic constriction the perfusion increased from  $30.2 \pm 8.3$  to  $40.3$  ml/100 g/min ( $p < 0.05$ ) (Fig 4). Perfusion of the nonischemic areas rose (Table 1) with each intervention. The endocardial-epicardial perfusion ratios were greater than one in control determinations and less than one in the ischemic areas after coronary occlusion. With the interventions the perfusion ratios did not change significantly (Table 1).

### DISCUSSION

In this study we used systolic thickening or thinning assessed echocardiographically to assess the function of acutely ischemic myocardium.  $PTs/PTd$  appears to be influenced strongly by the perfusion of the area of myocardium illuminated by the ultrasound beam, since wall thickening was seen in normally perfused areas and wall thinning was associated with the severe hypoperfusion of the ischemic areas.

Changes in afterload accomplished with any of the three interventions we used had beneficial effects on the thinning of acutely ischemic myocardium. Thinning was virtually abolished with norepinephrine and aortic constriction ( $S/PTd$  approached 1.0) and with methoxamine thickening of the initially ischemic wall occurred. These changes probably reflected improvement in the perfusion of the areas supplied by the occluded coronary artery; although perfusion of these areas was not restored to pre-occlusion levels significant increases in perfusion did occur with each intervention. Norepinephrine has positive inotropic effects and the improvement in  $PTs/PTd$  could be due to these. However, similar improvement occurred with methoxamine and aortic constriction which lack positive inotropic effects. This again suggests that the change in thickening was primarily due to improved perfusion. The reason for the increase in flow to the ischemic areas is not determined by this study. It may be due to increased collateral flow. Or, since the perfusion distribution after coronary occlusion is spatially and temporally heterogeneous, it may primarily reflect improved perfusion to normally perfused areas lying within the ischemic zone. A mixture of both these mechanisms is also possible.

Perfusion of the nonischemic areas also rose with the pressor interventions but unlike the ischemic posterior wall this was accompanied by small declines

## METHOXAMINE

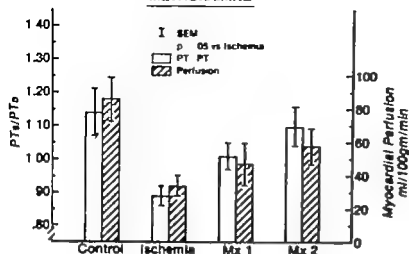


Fig 2 Effect of methoxamine on ischemic posterior wall thickening and perfusion SEM = standard error of the mean MX = methoxamine

## NOREPINEPHRINE

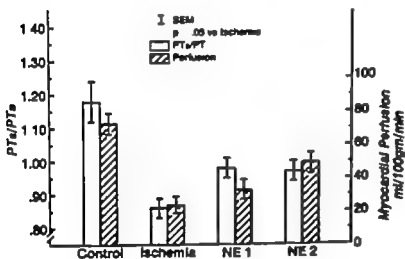


Fig 3 Effect of norepinephrine on ischemic posterior wall thickening and perfusion NE = norepinephrine

## AORTIC CONSTRICTION

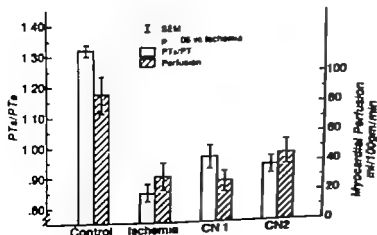


Fig 4 Effect of aortic constriction on ischemic posterior wall thickening and perfusion CN = aortic constriction

## REFERENCES

- 1 MILLIS L.D and BRAUNWALD E Myocardial ischemia New Engl J Med 296 1034 1977
- 2 SASAYAMA H FRANKLIN D ROSS J KEMPER W S and MCKOWY D Dynamic changes in left ventricular wall thickness and their use in analyzing cardiac function in the conscious dog A study based on a modified ultrasonic technique Am J Cardiol 38 870 1976
- 3 KERBER R E WILSON R.L and MARCUS M L An animal model for experimental echocardiographic studies J Clin Ultrasound 4 343 1976
- 4 KERBER R.E MARCUS M.L EHRHARDT J WILSON H and ABBOUD F M Correlation between echocardiographically demonstrated segmental dyskinesia and regional myocardial perfusion Circulation 52 1097 1975
- 5 KERBER, R E and ABBOUD F M Echocardiographic detection of regional myocardial infarction An experimental study Circulation 47 997 1973
- 6 FEIGENBAUM, H STONE J LEE D.A. MASSER W.K. and CHANG S Identification of ultrasound echoes from the left ventricle by use of intracardiac injections of indocyanine green Circulation 41 615 1970
- 7 MARCUS M.L KERBER R.E EHRHARDT J and ABBOUD F M Three-dimensional geometry of acutely ischemic myocardium Circulation 52 254 1975
- 8 MAROKO P R KJESKUS J.K SOBEL B E WATANABE T COVELL J W and ROSS J Jr Factors influencing infarct size following experimental coronary artery occlusion Circulation 43 67 1971
- 9 MAROKO, P R LIBBY P COVELL J W SOBEL B E ROSS J Jr and BRAUNWALD E Precordial ST segment alteration mapping An atraumatic method for assessing alterations in the extent of myocardial ischemic injury The effects of pharmacologic and hemodynamic interventions Am J Cardiol 29 223 1972
- 10 WATT H.L. DALUZ P WATERS D.D SWAN H J C and FORRESTER J S Contrasting influences of alterations in ventricular preload and afterload upon systemic hemodynamics function and metabolism of ischemic myocardium Circulation 55 318 1977
- 11 CORYA, B C RASMUSSEN S, FEIGENBAUM H KNOEBEL S B and BLACK M J Systolic thickening and thinning of the septum and posterior wall in patients with coronary artery disease congestive cardiomyopathy and atrial septal defect. Circulation 55 109 1977

in the thickening of the nonischemic septum (STs/STd). Thus, in nonischemic myocardium, perfusion alterations within a physiologic range are probably not a major determinant of myocardial function.

These results are compatible with other experimental studies. Elevation of coronary perfusion pressure has been shown to reduce the extent of myocardial damage after coronary occlusion in dogs (8,9). Hillis and Braunwald (1) suggest that this is because the deleterious effects of increased afterload on myocardial oxygen requirements are over-ridden by increases in collateral inflow to the ischemic area; the rich collateral network in dogs fosters this. Wyatt et al (10) showed that elevating arterial pressure with angiotensin produced an increase in coronary flow across an area of severe coronary stenoses, and this caused lactate production to shift to extraction. Systolic myocardial thinning probably will be useful to detect ischemia in patients. As noted, we found it to occur in severely hypoperfused areas in the animal. Corya et al (11) showed in humans that systolic thinning occurred only in regions of myocardial ischemia or fibrosis. In conditions such as atrial septal defect abnormalities of ventricular endocardial motion occurred but systolic thickening was preserved.

Our observations on the effect of increasing afterload must be applied with caution to patients. We assessed only the acute effects of the interventions; their long-term effects may not necessarily be similar. The coronary collateral network in humans is less extensive than the dog, and an increase in afterload in that situation may conceivably increase myocardial oxygen requirements out of proportion to the improvement in regional perfusion. The initial level of systolic pressure and the presence of left ventricular failure may also affect the response to afterload manipulations in patients.

#### ACKNOWLEDGEMENT

*The authors gratefully acknowledge the technical assistance of Margaret Schrader, Gil Koenigsascker, and Oscar Lim.*

*This work was supported by NIH Grant #HL014388 and RCDA #HL00328.*

This paper reviews the reliability of the echoventriculographic method by comparing it with cineangiographic and autopsy findings. Its clinical uses in the coronary care unit are outlined.

## PATIENTS

The accuracy of the echoventriculographic method in detecting regional asymmetry of the left ventricle was studied in 112 patients with acute or healed myocardial infarction. Correlations were made with electrocardiography in 70 patients, cineventriculography in 42 patients, and with autopsy from 17 patients. The normal series comprised of 42 healthy subjects (9).

## THE ECHOVENTRICULOGRAPHIC SCANNING TECHNIQUE

The most important matter in assessing the myocardial infarction by ultrasound is to determine the ultrasonic scanning sites in relation to the established anatomical landmarks of the left ventricle. First the beam direction is searched in which both the anterior and posterior mitral valve leaflets are recorded simultaneously (11). This basic beam direction is quite strictly defined in relation to the left ventricular anatomy. Above this beam direction the aortic root is used as a second fixed orientating point at the level of the mitral valve annulus. The apex is easy to find and serves as the most inferior scanning landmark in the vertical direction.

In the horizontal plane the reference points are the anterior junction of the right ventricular wall and the septum, the anterolateral and posteromedial edges of the mitral valve and the respective papillary muscles. The anterior wall motion is scanned at several levels by directing the transducer from the aortic root or mitral valve level towards the apex and from the septal regions over the anterior right ventricular junction laterally. The posterior wall is scanned at the upper and lower levels in relation to the mitral valve medially and laterally from the papillary muscle. A standardized method was developed to record 4 anterior and 4 posterior wall locations from 4 standard precordial positions (9, 11). Several additional positions are available according to the left ventricular enlargement.

At each precordial position the probe is aimed as perpendicular as possible to the underlying left ventricular endocardial surface (11). This is based on observing a parallel motion of echoes from different myocardial layers both in the A-mode and M-mode display. The upper septal and posterolateral walls are scanned from a precordial scanning position and axis (Fig. 1) (9).

## ACCURACY AND USEFULNESS OF ECHOVENTRICULOGRAPHY IN ACUTE MYOCARDIAL INFARCTION

M S NIEMINEN AND J HEIKKILÄ

*From the Cardiovascular Laboratory University Central Hospital  
SF-00290 Helsinki*

### SUMMARY:

Echoventriculography is a noninvasive and three-dimensional ultrasonic technique capable to assess in detail the regional performance of the left ventricle. Therefore the mechanical performance of the left ventricle after myocardial infarction is informatively assessed by the composite contributions made by infarcted and noninfarcted segments. Its reliability has been confirmed by direct cineangiographic and autopsy correlations. In clinical decision making such direct information is of great value both for diagnosis and therapeutic selection. In the coronary care unit echoventriculography provides most information obtained by the less feasible invasive cineangiographic examinations.

---

### INTRODUCTION

Echocardiography has become an important method of investigation in cardiology. Little information is available, however, on its use in patients with ischemic heart disease. Abnormalities of the segmental wall motions of the left ventricle are most common in these patients (4). A multidirectional single probe technique has been developed in our laboratory for detailed study of these regional wall motions. This scanning procedure, echoventriculography, describes the left ventricular performance by a composite picture made up from sequential studies of wall motions of the multiple ventricular segments. The method is capable of encompassing practically the entire left ventricle. Its success is based on the use of multiple precordial transducer sites and directions and on careful adjustment of gain and reject sets (11, 12).

Echoventriculography has proved to be useful and accurate technique for detection of the site and size of myocardial infarction. Function of the noninfarcted regions of the left ventricle is assessed at the same time.

# POSTINFARCTION ANTERO-APICO- INFERIOR ANEURYSM IN ECHO

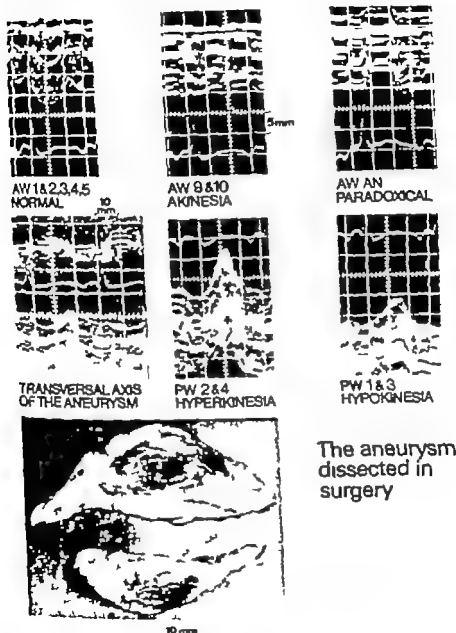
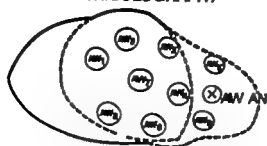


Fig. 1

Even more lateral areas are feasible in those cases where the left ventricle is enlarged into the lateral direction (9-11) (Fig. 1 AW AN and AW 8 to AW 14 in Fig. 5 in ref. 12). It is particularly rewarding to record these sites to years following large anterior or anterolateral infarction.



## ECHOVENTRICULOGRAPHY



ECG

V<sub>1</sub>V<sub>2</sub>V<sub>3</sub>V<sub>4</sub>V<sub>5</sub>V<sub>6</sub>V<sub>7</sub>V<sub>8</sub>V<sub>9</sub>V<sub>10</sub>V<sub>11</sub>V<sub>12</sub>V<sub>13</sub>V<sub>14</sub>V<sub>15</sub>V<sub>16</sub>V<sub>17</sub>V<sub>18</sub>V<sub>19</sub>V<sub>20</sub>V<sub>21</sub>V<sub>22</sub>V<sub>23</sub>V<sub>24</sub>V<sub>25</sub>V<sub>26</sub>V<sub>27</sub>V<sub>28</sub>V<sub>29</sub>V<sub>30</sub>V<sub>31</sub>V<sub>32</sub>V<sub>33</sub>V<sub>34</sub>V<sub>35</sub>V<sub>36</sub>V<sub>37</sub>V<sub>38</sub>V<sub>39</sub>V<sub>40</sub>V<sub>41</sub>V<sub>42</sub>V<sub>43</sub>V<sub>44</sub>V<sub>45</sub>V<sub>46</sub>V<sub>47</sub>V<sub>48</sub>V<sub>49</sub>V<sub>50</sub>V<sub>51</sub>V<sub>52</sub>V<sub>53</sub>V<sub>54</sub>V<sub>55</sub>V<sub>56</sub>V<sub>57</sub>V<sub>58</sub>V<sub>59</sub>V<sub>60</sub>V<sub>61</sub>V<sub>62</sub>V<sub>63</sub>V<sub>64</sub>V<sub>65</sub>V<sub>66</sub>V<sub>67</sub>V<sub>68</sub>V<sub>69</sub>V<sub>70</sub>V<sub>71</sub>V<sub>72</sub>V<sub>73</sub>V<sub>74</sub>V<sub>75</sub>V<sub>76</sub>V<sub>77</sub>V<sub>78</sub>V<sub>79</sub>V<sub>80</sub>V<sub>81</sub>V<sub>82</sub>V<sub>83</sub>V<sub>84</sub>V<sub>85</sub>V<sub>86</sub>V<sub>87</sub>V<sub>88</sub>V<sub>89</sub>V<sub>90</sub>V<sub>91</sub>V<sub>92</sub>V<sub>93</sub>V<sub>94</sub>V<sub>95</sub>V<sub>96</sub>V<sub>97</sub>V<sub>98</sub>V<sub>99</sub>V<sub>100</sub>V<sub>101</sub>V<sub>102</sub>V<sub>103</sub>V<sub>104</sub>V<sub>105</sub>V<sub>106</sub>V<sub>107</sub>V<sub>108</sub>V<sub>109</sub>V<sub>110</sub>V<sub>111</sub>V<sub>112</sub>V<sub>113</sub>V<sub>114</sub>V<sub>115</sub>V<sub>116</sub>V<sub>117</sub>V<sub>118</sub>V<sub>119</sub>V<sub>120</sub>V<sub>121</sub>V<sub>122</sub>V<sub>123</sub>V<sub>124</sub>V<sub>125</sub>V<sub>126</sub>V<sub>127</sub>V<sub>128</sub>V<sub>129</sub>V<sub>130</sub>V<sub>131</sub>V<sub>132</sub>V<sub>133</sub>V<sub>134</sub>V<sub>135</sub>V<sub>136</sub>V<sub>137</sub>V<sub>138</sub>V<sub>139</sub>V<sub>140</sub>V<sub>141</sub>V<sub>142</sub>V<sub>143</sub>V<sub>144</sub>V<sub>145</sub>V<sub>146</sub>V<sub>147</sub>V<sub>148</sub>V<sub>149</sub>V<sub>150</sub>V<sub>151</sub>V<sub>152</sub>V<sub>153</sub>V<sub>154</sub>V<sub>155</sub>V<sub>156</sub>V<sub>157</sub>V<sub>158</sub>V<sub>159</sub>V<sub>160</sub>V<sub>161</sub>V<sub>162</sub>V<sub>163</sub>V<sub>164</sub>V<sub>165</sub>V<sub>166</sub>V<sub>167</sub>V<sub>168</sub>V<sub>169</sub>V<sub>170</sub>V<sub>171</sub>V<sub>172</sub>V<sub>173</sub>V<sub>174</sub>V<sub>175</sub>V<sub>176</sub>V<sub>177</sub>V<sub>178</sub>V<sub>179</sub>V<sub>180</sub>V<sub>181</sub>V<sub>182</sub>V<sub>183</sub>V<sub>184</sub>V<sub>185</sub>V<sub>186</sub>V<sub>187</sub>V<sub>188</sub>V<sub>189</sub>V<sub>190</sub>V<sub>191</sub>V<sub>192</sub>V<sub>193</sub>V<sub>194</sub>V<sub>195</sub>V<sub>196</sub>V<sub>197</sub>V<sub>198</sub>V<sub>199</sub>V<sub>200</sub>V<sub>201</sub>V<sub>202</sub>V<sub>203</sub>V<sub>204</sub>V<sub>205</sub>V<sub>206</sub>V<sub>207</sub>V<sub>208</sub>V<sub>209</sub>V<sub>210</sub>V<sub>211</sub>V<sub>212</sub>V<sub>213</sub>V<sub>214</sub>V<sub>215</sub>V<sub>216</sub>V<sub>217</sub>V<sub>218</sub>V<sub>219</sub>V<sub>220</sub>V<sub>221</sub>V<sub>222</sub>V<sub>223</sub>V<sub>224</sub>V<sub>225</sub>V<sub>226</sub>V<sub>227</sub>V<sub>228</sub>V<sub>229</sub>V<sub>230</sub>V<sub>231</sub>V<sub>232</sub>V<sub>233</sub>V<sub>234</sub>V<sub>235</sub>V<sub>236</sub>V<sub>237</sub>V<sub>238</sub>V<sub>239</sub>V<sub>240</sub>V<sub>241</sub>V<sub>242</sub>V<sub>243</sub>V<sub>244</sub>V<sub>245</sub>V<sub>246</sub>V<sub>247</sub>V<sub>248</sub>V<sub>249</sub>V<sub>250</sub>V<sub>251</sub>V<sub>252</sub>V<sub>253</sub>V<sub>254</sub>V<sub>255</sub>V<sub>256</sub>V<sub>257</sub>V<sub>258</sub>V<sub>259</sub>V<sub>260</sub>V<sub>261</sub>V<sub>262</sub>V<sub>263</sub>V<sub>264</sub>V<sub>265</sub>V<sub>266</sub>V<sub>267</sub>V<sub>268</sub>V<sub>269</sub>V<sub>270</sub>V<sub>271</sub>V<sub>272</sub>V<sub>273</sub>V<sub>274</sub>V<sub>275</sub>V<sub>276</sub>V<sub>277</sub>V<sub>278</sub>V<sub>279</sub>V<sub>280</sub>V<sub>281</sub>V<sub>282</sub>V<sub>283</sub>V<sub>284</sub>V<sub>285</sub>V<sub>286</sub>V<sub>287</sub>V<sub>288</sub>V<sub>289</sub>V<sub>290</sub>V<sub>291</sub>V<sub>292</sub>V<sub>293</sub>V<sub>294</sub>V<sub>295</sub>V<sub>296</sub>V<sub>297</sub>V<sub>298</sub>V<sub>299</sub>V<sub>300</sub>V<sub>301</sub>V<sub>302</sub>V<sub>303</sub>V<sub>304</sub>V<sub>305</sub>V<sub>306</sub>V<sub>307</sub>V<sub>308</sub>V<sub>309</sub>

# POSTINFARCTION ANTERO-APICO-INFERIOR ANEURYSM IN ECHO

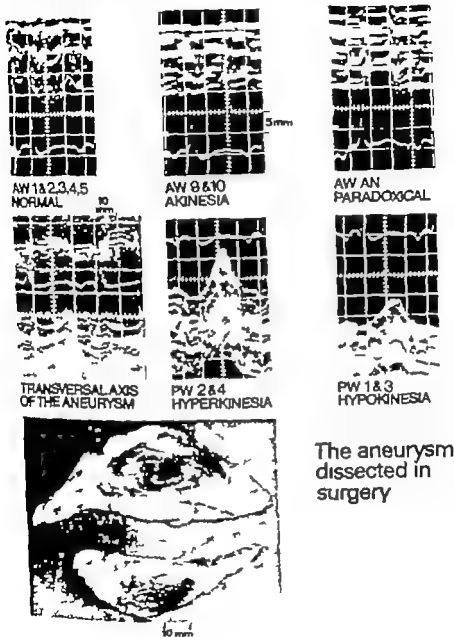
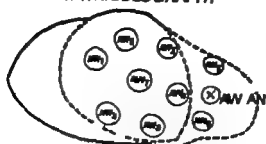


Fig 1

Even more lateral areas are feasible in those cases where the left ventricle is enlarged into the lateral direction (9 11) (Fig 1 AW AN and AW8 to AW14 in Fig 5 in ref 12). It is particularly rewarding to record these sites to detect ~~an~~ <sup>an</sup> following large anterior or anterolateral infarction.

## ECHOVENTRICULOGRAPHY



ECG

V<sub>1</sub>V<sub>2</sub>V<sub>3</sub>V<sub>4</sub>

LEFT CINEVENTRICULOGRAPHY

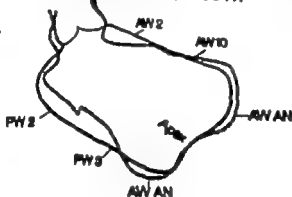
V<sub>5</sub>V<sub>6</sub>

Fig 1 In a postinfarction aneurysm the location of the different types of regional wall motion abnormalities recorded by echocardiography and cineangiography are in good agreement with each other and with Qs-complexes of the anterolateral electrocardiographic leads as well as the aneurysm sac dissected at surgery. The paradoxical bulging of the wall (AN AN) and the transversal axis (AN) of one of the two aneurysm sacs is shown measured from a point between location AN 9 and AN 10. Note the heavier N-mode lines of the stronger fibrous tissue echoes.

This position is achieved when the transducer is moved from the mitral valve recording position to the left edge of the sternum and directed inferiorly and posterolaterally. Position 2 is situated about 2 cm lateral to the mitral valve recording point: now the beam traverses both the free anterior and free posterior wall segments at the upper half of the left ventricle (locations AN2 and PW2 Fig 1). Position 3 of the probe is one intercostal space below position 1. It is used to study the low septal and the inferolateral walls of the left ventricle (locations AN3 and PW3 Fig 1). The low free anterior and inferoposterior locations (AN4 and PW4 Fig 1) are correspondingly scanned from position 4 (9). These standardized scanning locations are required to obtain reliable data in the repeated studies.

Additional positions are used for even more detailed estimation of the abnormalities of the left ventricular anterior wall motion. High anterior (AN5), apical (AN6) and midanteroseptal (AN7) sites are scanned from the respective positions on the chest wall (Fig 1).

## LATERAL NONTRANSMURAL INFARCTION IN ECHO

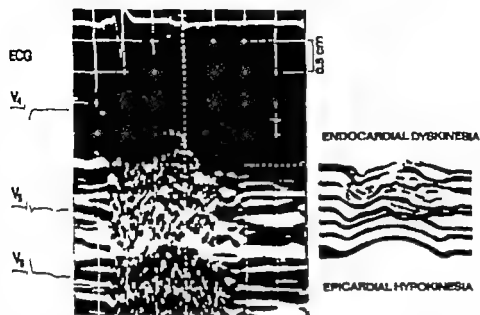


Fig 2. In acute subendocardial infarction the endocardial echo lines show dyskinetic motion while the epicardial layers contract in parallel way. The total motion is usually hypokinetic, the degree of which depends on the depth and severity of ischemia. Note the light echoes on the endocardial side with broken continuity during systole.

In contrast, the old lesion reflects the echoes in a uniform manner where the echolines move in parallel (Fig 1) during systole. The echoes reflected from scars are much stronger than those of normal myocardium and their motion is hypokinetic, akinetic or paradoxical depending on the depth of the lesion (Fig 1).

### RELIABILITY OF ECHOVENTRICULOGRAPHY IN ESTIMATION OF THE MYOCARDIAL INFARCTION

#### REPRODUCIBILITY OF REPEATED MEASUREMENTS

The reproducibility of the sequential measurements is achieved by strict standardization of probe directions relative of the anterior and posterior mitral valve leaflets and other anatomical reference sites mentioned. The accuracy in recording of the segmental wall motion is dependent on perpendicular directioning of the beam controlled by the parallel motion of myocardial echolines. When in repeated studies the patient is lying in exactly the same position, the standardized technique allows accurate and reproducible recordings. The axial resolution is theoretically less than 1 mm and in repeated studies the reproducibility of wall motion amplitude remained within 1 mm (9, 11, 12).

The sites at the posterior wall are usually scanned first the same gain and reject levels being employed for all sites A-mode echoes received from the posterior wall are positioned on the oscilloscope screen Fine adjustments are then made while the probe is moved slightly The echo patterns and necessary correlations are best observed in the A-mode display The probe is carefully rotated so that optimal endocardial epicardial and myocardial echoes are obtained with as few distortions as possible The motion-mode scannings are then recorded repeatedly on the memory scope and scannings of good quality are photographed with a Polaroid camera The anterior wall locations are recorded similarly but with a lower decibel gain value The amplitude of the regional wall motion mean systolic velocity and end systolic and diastolic wall thicknesses are measured (9) A quantitative echoventriculographic contraction index was developed for the left ventricular performance by summing up the individual regional wall amplitudes The index is obtained from the sum of the amplitudes of the 7 (12) or 8 (13) standard sites (PW1-4 and AW1-4 Fig 1) the sum is then normalized by dividing it by the sum of corresponding mean normal amplitudes (9)

Echoventriculography detects myocardial ischemia or infarction by the loss of contractile function at that segment (4 17) On the basis of the normal values obtained from 42 healthy subjects (9) the following criteria for asynergic wall motions are defined Wall motion is termed hyperkinetic when its systolic amplitude is over 6 mm at the anterior wall and over 10 mm at the posterior wall These values exceed the mean normal anterior and posterior segment amplitudes of 4.5 mm and 8.5 mm by 1 standard deviation In hypokinesia the amplitudes are below 3 mm at the anterior and below 6 mm at the posterior wall segments being less than normal minus 1 standard deviation An akinetic wall shows negligible motion while in paradoxically moving segments the wall motion is outward instead of the normal inward during the greater part of systole (10) Nor does any systolic thickening of an akinetic or paradoxically moving segment take place This is a useful sign when the physiological asynergy at the septal regions often present in well trained subjects must be excluded

#### DIFFERENTIATION BETWEEN AN OLD SCAR AND A RECENT INFARCTION

An old myocardial scar is a much stronger reflector of ultrasound than is myocardial necrosis A recently ischemic tissue is edematous it shows a broken continuity of the M-mode echolines in systole (Fig 2)

The major practical advantage of echo in the regional wall motion analysis compared to regional hemiaxis shortening percentages by cine is that it directly provides the contraction amplitudes in absolute values. These absolute motions however must be related to the size of the left ventricular cavity (13). On basis of these cineangiographic correlations, echoventriculography seems to be a reliable and sensitive method for the assessment of left ventricular function noninvasively (10). This index is applicable with contraction abnormalities.

#### CORRELATION WITH AUTOPSY FINDINGS

Echoventriculography was available in 17 patients with fatal myocardial infarction and of 11 more patients operated on for left ventricular aneurysm. The direct measurements at autopsy or at surgery confirmed that the site of the myocardial infarction may be determined very accurately by echoventriculography during life. The borders encompassing the infarcted myocardium was assessed by echo to fall into 7 sectors around the left ventricle. At autopsy variation over the predetermined sector was exceptional and usually the echo border was within 1 cm of that actually noted at autopsy. The same accuracy was achieved in the vertical direction on the size of infarct (H. N. to be published). Furthermore the capacity of ultrasound to differentiate old scars from fresh infarctions was confirmed by the pathological anatomical study. Old fibrous scars were dissected by echo from recent damage in every case. As yet this has not been possible with any other technique during life.

#### USEFULNESS OF ECHOVENTRICULOGRAPHY IN ACUTE MYOCARDIAL INFARCTION

##### REGIONAL MYOCARDIAL INFARCTION

Earlier the technical difficulties inhibited echoventriculographic studies of the anterior myocardial wall motion. With technical development of equipment and careful attention during the procedure the present method was successful in every patient in recording wall motions of the multiple posterior, septal, anterior and lateral left ventricular segments. Attention has been recently paid by other investigators also to recording of multiple segments of the left ventricle. Corya et al reported a success rate of 83% with a somewhat simpler recording technique (1). The present echoventriculographic method scans multiple segments around the entire left ventricle. It provides a means to assess the

## CORRELATION WITH ELECTROCARDIOGRAPHY

Echocardiography and electrocardiography have agreed in every case on the anterior or posterior site of the acute myocardial infarction. We have reported these relationships in detail earlier (4) and now the same good correlation is available in 70 patients. In anterior infarctions the relationship was good also quantitatively. The more precordial leads showed infarction pattern the more asynergic segments were noted in echo (4) (Fig 1). The estimation of the size of inferoposterior infarction by electrocardiography was less accurate with the few depicting leads available than by the echo scanning. Echo also demonstrated the inferoposterior lesion to often extend into a posterolateral direction when ECG showed inferior damage only. This slight difference is similar to that found in correlation of electrocardiograms with the autopsy data (7).

## CORRELATION WITH CINEANGIOGRAPHY

Echocardiography was compared with cineangiographic study of left ventricular function in 42 patients. They had coronary artery disease and were studied for bypass surgery (10). Abnormal regional contraction was noted in 33 of the 42 patients by single plane cineangiography performed in the right anterior oblique projection. Any asynergic contraction noted in angiography was always correctly detected by echo. Segments contracting normally in echo did so also in cine. Besides this qualitative accuracy the degree of asynergic motion agreed with both methods (10). Echo was further able to scan left ventricular dysfunction in all these patients in those regions that do not become visualized in the single plane cine. Hyperkinesia of the uninvolved areas was more readily detected by echo than by cine (30 vs 14 patients).

Cineangiographic and echocardiographic contraction indices were developed for quantitative purposes (10). The overall correlation between them in the whole series was significant ( $r=0.62$ ,  $P<0.005$ ). The main reason for the weakening of the correlation was found to be the presence of either large apical asynergy or apical hyperkinesia. Those cases excluded the correlation between the cine and echo contraction indices was very good ( $r=0.91$ ,  $p<0.05$ ).

The reliability of ejection fraction measurement by echo from the standard minor axis was not found to be good in the asynergic ventricles in relation to ejection fraction by area length method from cineangiography ( $r=0.38$ ) (10).

severe infarctions from those with severe power failure or fatal course ( $r = 0.79$   $p < 0.001$ ) (14). In uncomplicated infarctions it was  $78 \pm 12\%$  of the normal with moderate left heart failure  $55 \pm 14\%$  while in severe power failure being only  $35 \pm 14\%$  (8). This index brings out clearly the team work of the infarcted and the noninfarcted ventricular segments. When the healthy segments contract vigorously the index is higher and the prognosis usually good. The larger the paradoxical area the poorer the contraction of the noninfarcted myocardium the lower is the index (14). This contraction index summed from the multiple ventricular sites also correlated with the echocardiographic ejection fraction ( $r = 0.60$   $p < 0.005$ ).

#### FUNCTION OF THE NONINFARCTED MYOCARDIUM

The function of the healthy myocardium was hypercontractile in 12 of the 30 patients (40%) but this occurred only in the uncomplicated ( $+27\%$  over normal) and moderately severe infarctions ( $+4\%$ ) (13).

The 4 patients who died in the group of 10 with pump failure had a very poor regional contraction index. It remained below 50% in all of them whose ejection fractions were below 30%. Remarkably hyperkinesia was not detected at any noninfarcted site in the 10 patients with pump failure (14). The failure of the uninvolved myocardium to develop even a normal response obviously contributed to power failure in these patients. The mean contraction index of this uninvolved region was 79% of normal ( $p < 0.005$ ) (14).

The two modes of function in the noninfarcted myocardial segments revealed by echo are pathophysiologically important. First in uncomplicated infarctions these segments seemed to contract unnecessarily vigorously probably under excessive adrenergic drive (14). Use of beta blocking drugs in these patients would logically protect markedly ischemic but not yet infarcted segments (5). Secondly in large infarctions the vigorous compensating motion of the noninfarcted segments is obviously necessary for adequate pump function and survival (14). All those patients who had severe pump failure or died failed to show compensatory motion of the noninfarcted myocardium. Inadequate segmental response occurred even despite therapeutic inotropic support (13, 14). In this setting of failing uninvolved segments even a small reinfarction carries a poor prognosis. These implications of the functional state of the noninfarcted segments have been so far largely overlooked in acute myocardial infarction.



contribution of individual segments to the overall left ventricular function which has not been possible so far non invasively. The accuracy of technique in locating and quantifying either noncontractile or hyperfunctioning segments has been convincingly documented in the correlative studies with electrocardiogram cineangiographic analysis and autopsy data discussed above (4 10 11 12 13 14) (Fig 1)

Abnormal wall motion of the infarcted region occurred in each of the 30 consecutive patients with acute myocardial infarction (4). Asynergy was seen during the first hours of infarction and was often noted to precede the Q wave development in the serial ECG. Serial studies were made on 24 patients during the first week in hospital (12). In anterior infarctions the asynergic contraction was generally maximal already on the 1st day. The amplitude of the systolic paradoxical outward motion of the infarcted segment was  $3.2 \pm 3.0$  mm without any later improvement. Instead the border areas showed some improvement in 4 of the 8 anterior infarctions.

In posterior infarctions paradoxical motion was an exception; nevertheless a remarkable reduction of wall motion occurred at the posterior infarcted sites in every patient (4 3). The wall motion was most commonly akinetic; the lowest wall motion mean amplitude of  $1.9 \pm 2.3$  mm was seen on the 3rd postinfarction day (13). However no recovery has been observed in those patients with fatal infarction (13 15). The number of sites showing abnormal motion was smaller in posterior infarctions where the wall motion was most commonly akinetic (13).

The above differences in the regional performance between the anterior and posterior infarctions are in good agreement with the enlargement of the left ventricle in these groups (13). The left ventricular cavity size was enlarged in 62% of the 30 consecutive patients. Such loss of segmental left ventricular function (6) agrees nicely also with the haemodynamic dysfunction which is more serious in anterior than in posterior infarctions (16).

#### QUANTITATIVE ASSESSMENT OF REGIONAL WALL MOTION

Mechanical performance of the left ventricular segments related well with the clinical severity of acute myocardial infarction. Two basic factors operate here: size of the asynergic region and the compensating ability of the noninfarcted myocardium. The echoventriculographic contraction index by uniting these two factors clearly separated the patients with uncomplicated and moderately

10. ILENTIKEN M S Echoventriculography in chronic coronary heart disease Correlation with single-plane cineangiography of the left ventricle *Europ J Cardiol* 11 1977 (in press)
11. ILENTIKEN M S Applications of multidirectional echocardiography in myocardial infarction Academic dissertation University of Helsinki 1977
12. ILENTIKEN M S Technical aspects of single beam ultrasound regurgitation *Acta Med Scand* 1977
13. ILENTIKEN M S HEIKKILÄ J Echoventriculography in acute myocardial infarction II Monitoring of left ventricular performance *Brit Heart J* 39 271 1976
14. ILENTIKEN M S HEIKKILÄ J Echoventriculography in acute myocardial infarction III Clinical correlations and implication of the noninfarcted myocardium *Amer J Cardiol* 38 1 1976
15. BATHINI R A RACKLEY C E RUSSELL R O Jr Serial evaluation of left ventricular volumes and posterior wall movement in the acute phase of myocardial infarction using ultrasound *Amer J Cardiol* 29 286 1973
16. RUSSELL R O Jr HUNT D RACKLEY C E Left ventricular hemodynamics in anterior and inferior myocardial infarction *Amer J Cardiol* 32 8 1973
17. THEROUX P FRANKLIN D ROSS J Jr KEMPER W S Regional myocardial function during acute coronary occlusion and its modification by pharmacological agents in the dog *Circulation Res* 35 896 1975

## FURTHER APPLICATIONS

Recently the ultrasound technique has been a highly rewarding tool in experimental studies on the effects of pharmacological interventions in acute myocardial infarction (17). We have applied this concept in patients with acute myocardial infarction (5). The directional changes taking place in the ST segment mapping were noted to agree with the segmental wall motions visualized by echo. The ischemic zones bordering the infarction instantaneously showed either stronger contraction or more marked dysfunction along with increase or decrease of ST segments deviations or chest pain (5). The myocardial segmental function reveals the effects of drugs on left ventricular dynamics instantaneously and more sensitively than the haemodynamic changes. In patients with ongoing ischemic state this technique seems to detect very sensitively and rapidly any favourable or deleterious effect of a drug intervention.

## ACKNOWLEDGEMENT

*This work was partly supported by the Paulo Bauer Foundation, the Paulo Foundation and the Ida Montin Foundation.*

## REFERENCES

- 1 CORYA B C Applications of echocardiography in acute myocardial infarction. In: Innovation in the diagnosis and management of acute myocardial infarction. Editors Brest A M, Wiener L, Chung E K and Kasparian H. A Davis Co. Philadelphia 1975. p 113-127.
- 2 CORYA B C, RASMUSSEN S, FEIGENBAUM H, BLACK M J and KNOCKEL S B. Echocardiographic detection of scar tissue in patients with coronary artery disease. (Abstract). Amer J Cardiol 37: 129, 1976.
- 3 EDLER I. Ultrasoundcardiography. Acta Med Scand Suppl 370, 1961.
- 4 HEIKKILÄ J, NIEMINEN M S. Echoventriculographic detection, localization and quantification of left ventricular asynergy in acute myocardial infarction. Brit Heart J 37: 46, 1975.
- 5 HEIKKILÄ J, TABAKIN B S, HUGENHOLTZ P G. Quantification of function in normal and infarcted regions of the left ventricle. Cardiovasc Res 6: 516, 1972.
- 6 HEIKKILÄ J, NIEMINEN M S. Noninvasive monitoring of infarct size in man. Abstract. 7th European Congress of Cardiology 1976.
- 7 HORAN L G, FLOWERS M C, TALLESON W J and THOMAS J R. Significance of the diagnostic Q wave of myocardial infarction. Circulation 43: 428, 1971.
- 8 KILLIP T. Coronary care units and current policies and results. In: Acute Myocardial Infarction. Editors Julian D C, Oliver M F. E & S Livingstone, New York. p 23, 1968.
- 9 NIEMINEN M S. Normal left echoventriculography. Ann Clin Res 7: 1, 1975.

## INTRODUCTION

M-mode echocardiography has proven to be a valuable method for estimating ventricular volume and describing various parameters of ventricular function in the symmetrically contracting normally shaped left ventricle (1-5). The M-mode echocardiogram provides the basic data from which these determinations are generated by recording the path of the ultrasonic beam as it traverses the left ventricular cavity from the endocardial surface of the interventricular septum to the corresponding endocardial surface of the left ventricular posterior wall. In order to relate this basic distance or dimensions to global left ventricular size or function a number of assumptions must first be made. It must be assumed that 1) the echocardiographic diameter of the ventricle represents a true minor dimension or axis of the ventricular chamber, 2) the left ventricle is circular in its short axis configuration and hence the measured minor dimension is equal in all planes, 3) the left ventricle conforms to a selected geometric shape in which the minor dimension measured from the echocardiogram bears a fixed relationship to the major or long axis of the geometric model and 4) that the function of the ventricle in the area recorded is reflective of overall left ventricular function (6).

In the majority of cases these assumptions have proven to be essentially correct and hence estimation of left ventricular volume and function from a single minor dimension of the ventricle valid. In specific clinical situations however the shape of the ventricle may be altered so that it no longer conforms to the assumed geometric model. In these cases data relative to left ventricular volume and global function based on the previously noted assumptions will of necessity be inaccurate (5,6).

Changes in ventricular shape may be either symmetric affecting the entire left ventricle or localized to a specific portion of the ventricle. When there is a change in overall ventricular shape the recorded echocardiographic dimension will also be effected. In this regard Teichholz et al (7) noted an increase in the length to diameter ratio in small ventricles and a corresponding decrease in this ratio in larger more spherical ventricles. Since the length/diameter ratio and, hence shape was a function of the diameter (or echocardiographic dimension) the variation in shape could be appreciated and corrected for appropriately.

# CROSS-SECTIONAL ECHOCARDIOGRAPHIC EVALUATION OF CHANGES IN VENTRICULAR SHAPE IN THE ISCHAEMIC AND NON ISCHAEMIC LEFT VENTRICLE

A E WEYMAN,

*From the Kramert Institute of Cardiology the Department of Medicine  
Indiana University School of Medicine and the Veterans Administration  
Hospital Indianapolis Indiana*

## SUMMARY:

M-mode echocardiography is a useful method for estimating left ventricular volumes and determining multiple parameters of left ventricular function in the symmetrically contracting normally shaped ventricle. In many clinical situations however the shape of the ventricle may be altered or distorted in such a way that the basic M-mode diameter or dimension of the ventricle is no longer reflective of overall left ventricular volume or function.

Cross-sectional echocardiography is a valuable method for detecting abnormalities in left ventricular shape and thereby defining those cases in which the M-mode method may not accurately reflect ventricular size or performance. In this report two examples of abnormalities in ventricular shape are described. These include the marked alteration in left ventricular conformation which occurs when aneurysm formation complicates ischemic heart disease and the more subtle changes in ventricular shape seen in patients with both absolute and relative right ventricular volume overload due to alteration in septal position. These examples illustrate the value of cross-sectional echocardiography in defining abnormalities of left ventricular shape; indicating situations in which the M-mode echocardiographic determinations of ventricular volume and function may be misleading and explaining changes in the patterns of wall motion observed by M-mode echocardiography which are due to alterations in the shape of the left ventricle.

## INTRODUCTION

M-mode echocardiography has proven to be a valuable method for estimating ventricular volume and describing various parameters of ventricular function in the symmetrically contracting normally shaped left ventricle (1-5). The M-mode echocardiogram provides the basic data from which these determinations are generated by recording the path of the ultrasonic beam as it traverses the left ventricular cavity from the endocardial surface of the interventricular septum to the corresponding endocardial surface of the left ventricular posterior wall. In order to relate this basic distance or dimensions to global left ventricular size or function a number of assumptions must first be made. It must be assumed that 1) the echocardiographic diameter of the ventricle represents a true minor dimension or axis of the ventricular chamber, 2) the left ventricle is circular in its short axis configuration and hence the measured minor dimension is equal in all planes, 3) the left ventricle conforms to a selected geometric shape in which the minor dimension measured from the echocardiogram bears a fixed relationship to the major or long axis of the geometric model and 4) that the function of the ventricle in the area recorded is reflective of overall left ventricular function (6).

In the majority of cases these assumptions have proven to be essentially correct and hence estimation of left ventricular volume and function from a single minor dimension of the ventricle valid. In specific clinical situations however the shape of the ventricle may be altered so that it no longer conforms to the assumed geometric model. In these cases data relative to left ventricular volume and global function based on the previously noted assumptions will of necessity be inaccurate (5,6).

Changes in ventricular shape may be either symmetric affecting the entire left ventricle or localized to a specific portion of the ventricle. When there is a change in overall ventricular shape the recorded echocardiographic dimension will also be effected. In this regard Teichholz et al (7) noted an increase in the length to diameter ratio in small ventricles and a corresponding decrease in this ratio in larger more spherical ventricles. Since the length/diameter ratio and hence shape was a function of the diameter (or echocardiographic dimension) the variation in shape could be appreciated and corrected for appropriately.

When change in ventricular shape is localized however it may either not effect the echocardiographic dimension or produce an effect which is not proportionate to the magnitude of the overall structural abnormality. In these cases it will not be possible to appropriately assess the ventricular volume using the M-mode echocardiographic dimension or perhaps more significantly to recognize the fact that this error has occurred. The most common example of this is the patient with ischemic heart disease in whom a large area of ventricular dyskinesis or aneurysm formation may be present and yet in whom the standard echocardiographic dimension at the base of the heart may be normal. In this manuscript we will discuss the role of cross sectional echocardiography in detecting localized abnormalities of left ventricular shape which may either be inapparent on the M-mode record or when present may be unappreciated as being due to a change in the shape of the ventricle.

## 1 ABNORMALITIES OF LEFT VENTRICULAR SHAPE - ISCHEMIC HEART DISEASE

The most striking distortion in left ventricular shape is the ventricular aneurysm. These aneurysms by definition distort both the systolic and diastolic shape of the ventricle and may vary in size from small, functionally insignificant, localized abnormalities to massive distortions of ventricular structure which underly severe cardiac decompensation. Since aneurysm formation may complicate as many as 10 % of acute transmural myocardial infarctions and underlie such major complications as recurrent ventricular tachyarrhythmias, systemic emboli and intractable congestive heart failure, all of which adversely effect prognosis, their detection is of major importance (8, 9, 10).

The M-mode echocardiogram has not proven to be a useful method for detecting ventricular aneurysms. Despite the common occurrence of these lesions, data suggesting that the M-mode technique might detect aneurysms has appeared only in the form of isolated case reports (11, 12). This occurs because aneurysms arise most commonly in areas of the ventricle such as the cardiac apex which are poorly recorded by the M-mode system. In addition, in order to appreciate the change in shape of any geometric figure it is generally necessary to be able to visualize the spatial configuration of the entire figure and not merely a localized portion.

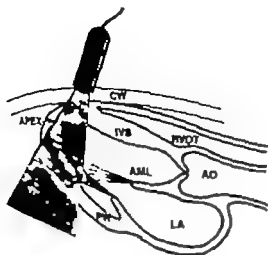


Fig 1 Cross-sectional echocardiographic recording of a long axis of the cardiac apex. The normal tapering of the endocardium in the region of the cardiac apex together with the separation between the endocardial and epicardial interfaces reflective of wall thickness are apparent. CV = chest wall. IVS = interventricular septum. RVOT = right ventricular outflow tract. AO = aorta. AML = anterior mitral leaflet. LA = left atrium. PV = posterior left ventricular wall.

The advent of two-dimensional or cross sectional echocardiography enhanced our ability to detect ventricular aneurysms in several ways. First, as previously noted, the cross sectional technique expands greatly the area of the heart which is available for examination. By adding the cardiac apex as well as the medial and lateral walls of the left ventricle to the areas available for study, this technique permits examination of the total left ventricle. The ability to record the cardiac apex is of particular importance since fully 80% of coronary artery disease associated aneurysms will involve this area. Secondly, by displaying the acoustic data in a spatially oriented format, the configuration of the long and short axes of the ventricle can be visualized and distortions in shape appreciated by their inappropriate relationship to more normal adjacent areas and/or variation from established normal ventricular configuration. Finally, by adding dynamic motion to the display, differences in contraction patterns between adjacent areas can be observed which further highlight spatial distortion.

The earlier reports indicated that localized areas of asynergy or aneurysmal dilatation could be detected in selected patients using the B-mode scanning technique. Teichholz et al (13) recorded B-mode scans of the left ventricle in 14 patients with localized ventricular asynergy and demonstrated a good correlation between the echocardiographic and angiographic detection of these regions. Similarly, Yoshikawa et al (14) although unable to detect ventricular aneurysms using M-mode echocardiography, were able to visualize areas of ventricular distortion in each of 15 patients using the B-mode scanning technique. In a more recent study to examine the ability of real time cross sectional echocardiography to

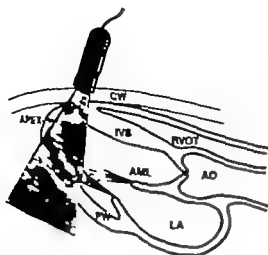


When change in ventricular shape is localized however it may either not effect the echocardiographic dimension or produce an effect which is not proportionate to the magnitude of the overall structural abnormality. In these cases it will not be possible to appropriately assess the ventricular volume using the M-mode echocardiographic dimension or perhaps more significantly to recognize the fact that this error has occurred. The most common example of this is the patient with ischemic heart disease in whom a large area of ventricular dyskinesis or aneurysm formation may be present and yet in whom the standard echocardiographic dimension at the base of the heart may be normal. In this manuscript we will discuss the role of cross sectional echocardiography in detecting localized abnormalities of left ventricular shape which may either be inapparent on the M-mode record or when present may be unappreciated as being due to a change in the shape of the ventricle.

## 1. ABNORMALITIES OF LEFT VENTRICULAR SHAPE ISCHEMIC HEART DISEASE

The most striking distortion in left ventricular shape is the ventricular aneurysm. These aneurysms by definition distort both the systolic and diastolic shape of the ventricle and may vary in size from small functionally insignificant localized abnormalities to massive distortions of ventricular structure which underlie severe cardiac decompensation. Since aneurysm formation may complicate as many as 10 % of acute transmural myocardial infarctions and underlie such major complications as recurrent ventricular tachyarrhythmias, systemic emboli, and intractable congestive heart failure, all of which adversely effect prognosis, their detection is of major importance (8, 9, 10).

The M-mode echocardiogram has not proven to be a useful method for detecting ventricular aneurysms. Despite the common occurrence of these lesions, data suggesting that the M-mode technique might detect aneurysms has appeared only in the form of isolated case reports (11, 12). This occurs because aneurysms arise most commonly in areas of the ventricle such as the cardiac apex which are poorly recorded by the M-mode system. In addition, in order to appreciate the change in shape of any geometric figure it is generally necessary to be able to visualize the spatial configuration of the entire figure and not merely a localized portion.



*Fig 1 Cross-sectional echocardiographic recording of a long axis of the cardiac apex. The normal tapering of the endocardium in the region of the cardiac apex together with the separation between the endocardial and epicardial interfaces reflective of wall thickness are apparent CW = chest wall IVS = interventricular septum RVOT = right ventricular outflow tract AO = aorta AML = anterior mitral leaflet LA = left atrium PV = posterior left ventricular wall*

The advent of two-dimensional or cross sectional echocardiography enhanced our ability to detect ventricular aneurysms in several ways. First as previously noted the cross sectional technique expands greatly the area of the heart which is available for examination. By adding the cardiac apex as well as the medial and lateral walls of the left ventricle to the areas available for study this technique permits examination of the total left ventricle. The ability to record the cardiac apex is of particular importance since fully 80% of coronary artery disease associated aneurysms will involve this area. Secondly by displaying the acoustic data in a spatially oriented format the configuration of the long and short axes of the ventricle can be visualized and distortions in shape appreciated by their inappropriate relationship to more normal adjacent areas and/or variation from established normal ventricular configuration. Finally by adding dynamic motion to the display differences in contraction patterns between adjacent areas can be observed which further highlight spatial distortion.

Two earlier reports indicated that localized areas of asynergy or aneurysmal dilatation could be detected in selected patients using the B-mode scanning technique. Teichholz et al (13) recorded B-mode scans of the left ventricle in 14 patients with localized ventricular asynergy and demonstrated a good correlation between the echocardiographic and angiographic detection of these regions. Similarly Yoshikawa et al (14) although unable to detect ventricular aneurysms using M-mode echocardiography were able to visualize areas of ventricular distortion in each of 15 patients using the B-mode scanning technique. In a more recent study to examine the ability of real time cross-sectional echocardiography to

When change in ventricular shape is localized however it may either not effect the echocardiographic dimension or produce an effect which is not proportionate to the magnitude of the overall structural abnormality. In these cases it will not be possible to appropriately assess the ventricular volume using the M-mode echocardiographic dimension or perhaps more significantly to recognize the fact that this error has occurred. The most common example of this is the patient with ischemic heart disease in whom a large area of ventricular dyskinesis or aneurysm formation may be present and yet in whom the standard echocardiographic dimension at the base of the heart may be normal. In this manuscript we will discuss the role of cross sectional echocardiography in detecting localized abnormalities of left ventricular shape which may either be inapparent on the M-mode record or when present may be unappreciated as being due to a change in the shape of the ventricle.

#### 1 ABNORMALITIES OF LEFT VENTRICULAR SHAPE ISCHEMIC HEART DISEASE

The most striking distortion in left ventricular shape is the ventricular aneurysm. These aneurysms by definition distort both the systolic and diastolic shape of the ventricle and may vary in size from small functionally insignificant localized abnormalities to massive distortions of ventricular structure which underlie severe cardiac decompensation. Since aneurysm formation may complicate as many as 10 % of acute transmural myocardial infarctions and underlie such major complications as recurrent ventricular tachyarrhythmias, systemic emboli and intractable congestive heart failure, all of which adversely effect prognosis, their detection is of major importance (8, 9, 10).

The M-mode echocardiogram has not proven to be a useful method for detecting ventricular aneurysms. Despite the common occurrence of these lesions, data suggesting that the M-mode technique might detect aneurysms has appeared only in the form of isolated case reports (11, 12). This occurs because aneurysms arise most commonly in areas of the ventricle such as the cardiac apex which are poorly recorded by the M-mode system. In addition, in order to appreciate the change in shape of any geometric figure it is generally necessary to be able to visualize the spatial configuration of the entire figure and not merely a localized portion.

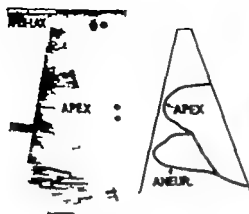


Fig 4: Long axis cross-sectional study of the cardiac apex and posterior wall demonstrating a large posterior wall aneurysm. This aneurysm extended from the area of the papillary muscle to the A-ring at the base of the heart. (From Heyman A E et al Detection of Left Ventricular Aneurysms by Cross-Sectional Echocardiography *Circulation*, 54:936 1976)



Fig 5: Left ventricular angiogram corresponding to the cross-sectional study in Fig 4. Again the large aneurysm of the posterior wall of the ventricle is apparent. (From Heyman A E et al Detection of Left Ventricular Aneurysms by Cross-Sectional Echocardiography *Circulation* 54 936 1976)

there is initial motion of the apex toward the base of the heart together with symmetrical motion of the anterior and posterior left ventricular walls toward the geometric center of the ventricle. In contrast in patients with apical aneurysms a clearly defined localized interruption in the diastolic configuration of the left ventricular apex was noted. This distortion in shape either remained constant or increased during ventricular systole.

Fig 2 is a recording from a patient with a large anteroapical aneurysm illustrating the change in ventricular shape seen with these lesions. The right hand panel of this figure is a line drawing which compares the observed pattern of left ventricular apical shape (solid line) with the expected normal contour of the left ventricular apex (interrupted line). Fig 3 is an angiographic recording of the left ventricle from the same patient illustrating the similarity of apical contour recorded by these two imaging techniques.

Although the cardiac apex is the area most frequently involved in ventricular aneurysm formation these lesions may occur in any area of the left ventricle. Fig 4 is a cross sectional recording from a patient with an extensive posterior inferior aneurysm. This aneurysm produces a marked alteration

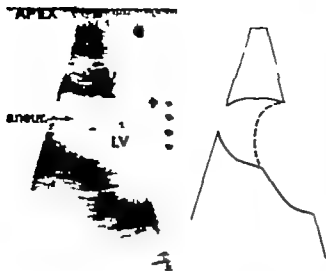


Fig 2 Long axis cross-sectional study of the left ventricular apex from a patient with a moderately large apical aneurysm. The tip of the apex is to the left of the figure while the body of the left ventricle is to the right. The vertical arrow indicates the junction of aneurysmal segment with the normal left ventricle. The solid line indicates the recorded contour of the left ventricular apex while the interrupted line indicates the expected contour if the normal curvatures of the body of the left ventricle were extended. Interruption of the normal curva-

ture of the left ventricle by the ventricular aneurysm is apparent. (From Heyman et al. Detection of Left Ventricular Aneurysms by Cross-Sectional Echocardiography. *Circulation* 54:936, 1976.)



Fig 3 Left ventricular cineangiogram corresponding to the cross-sectional study in fig 2. The apex in the angiographic study is reversed in comparison to the cross-sectional recording. The sector superimposed on this angiogram illustrates the relationship of the 30° scan to the left ventricular apex with the transducer placed directly over the apical

area. The area of the ventricle encompassed in this 30° sector corresponds to the similar area in the sector in fig 2. (From Heyman A E et al. Detection of Left Ventricular Aneurysm by Cross-Sectional Echocardiography. *Circulation* 54:936, 1976.)

detect ventricular aneurysms we studied 31 consecutive patients with angiographically proven left ventricular aneurysms (15). In this study 87 % of the aneurysms were confined to or involved the cardiac apex. In each of these 31 cases it was possible to visualize the aneurysm with the cross sectional technique thus permitting its presence, location, and in the majority of cases, extent to be determined. Fig 1 is a cross sectional recording of the cardiac apical area illustrating the normal configuration of the endocardial and epicardial surfaces, myocardial thickness and tapering of the ventricular myocardium in the region of the apex. During normal contraction

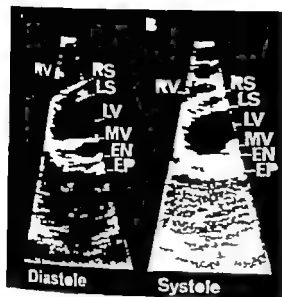


Fig 8 Normal short axis cross-sectional study of the body of the left ventricle at the level of the mitral valve. The left hand panel is recorded during diastole and illustrates the normal circular configuration of the left ventricle and interventricular septum. In the right hand panel recorded during systole there is progressive inward motion of the entire endocardial surface of the left ventricle toward the geometric center of the ventricular cavity with diminution in cavity size and increase in ventricular myocardial thickness. RV = right ventricle, RS = right side of the interventricular septum, LS = left side

of the interventricular septum, LV = left ventricular cavity, MV = mitral valve, EN = endocardium, EP = epicardium. (From Weyman A.E. et al. Mechanism of Abnormal Septal Motion in Patients with Right Ventricular Volume Overload. *Circulation* 54:179, 1978)

tional system by defining the subgroup of patients with distortion in ventricular shape produced by ventricular aneurysms adds directly to our clinical knowledge and also is of indirect value by helping to exclude patients in whom M-mode estimations of ventricular function would be misleading.

## 2. ABNORMALITIES OF LEFT VENTRICULAR SHAPE IN THE NON ISCHEMIC LEFT VENTRICLE

In addition to abnormalities of left ventricular shape occurring as a result of aneurysmal bulging of the left ventricular wall, significant change in ventricular shape may also be produced by extrinsic compression or invagination of the left ventricle. This type of abnormality of shape is most commonly produced by alteration in the position of the interventricular septum. The original indication that abnormalities of ventricular shape might be due to alteration in septal position arose from the observation that in patients with right ventricular volume overload and paradoxical septal motion the left ventricular internal diameter frequently increased in the early portion of systole. If in these cases the ventricular diameter was an appropriate indicator of left ventricular volume then the volume of the ventricle would be increasing rather than decreasing during this phase of the cardiac cycle.

Since an increase in volume during systole was impossible it was concluded that the ventricular diameter was no longer reflective of the ventricular volume and hence that a change in ventricular shape must have occurred.

LV-LA

LV

AO

Fig 6 Long axis cross-sectional scan of the body of the left ventricle demonstrating a small circular echo-free space beneath the posterior wall of the left ventricle with apparent continuity between the echo-free space and the cavity of the left ventricle (From Estevez C M et al Detection of Left Ventricular Diverticulum by Cross-Sectional Echocardiography Chest 69 644 1978)

Fig 7 Long ventricular angiogram demonstrating a small localized diverticulum of the inferior wall of the left ventricle corresponding in appearance and location to the cross-sectional scan recorded in fig 6 (From Estevez et al Detection of Left Ventricular Diverticulum by cross-sectional echocardiography Chest 69 644 1978)

the ventricle Fig 5 is an angiographic recording from the same patient again illustrating the similarity in appearance of the aneurysm by angiography and cross sectional echocardiography

in the posterior surface of the left ventricle extending from the posterior papillary muscle to the AV ring and involving the entire posterior surface of

In addition to large coronary artery disease associated aneurysms it is also possible to record more discrete alterations of left ventricular shape (16) Fig 6 and 7 are a cross sectional scan and left ventricular angiogram from a patient with a small congenital left ventricular diverticulum The diverticulum as well as its communication with the left ventricular cavity are apparent from the cross-sectional recording

When the M-mode recordings in the same group of patients were examined the presence of an aneurysm based on an increase in ventricular diameter at the apex compared to the standard basal dimension was suggested in only 47 % of the cases (15) Furthermore these criteria were only applicable to patients with apical aneurysms with the result that aneurysms localized elsewhere in the ventricle were undetected by the M-mode technique Thus the cross sec



Fig 10 Serial short axis cross-sectional echograms of the body of the left ventricle in the region of the mitral valve beginning at end systole and extending through the diastolic filling period to end diastole. The line drawing in the center of the figure illustrates the relative positions of the left ventricular endocardium at the various portions of the diastolic filling phase. At the end of systole the left ventricle is in its normal circular configuration (1). Immediately following at the onset of diastolic filling (2) there

is a marked inward motion of the interventricular septum toward the body of the left ventricle which changes the shape of the left ventricle. As diastole progresses (3 and 4) the ventricle gradually returns to its more normal circular configuration. This return of the ventricle to normal shape is produced by gradual anterior and rightward motion of the interventricular septum back away from the body of the left ventricle toward its normal position (i.e. curving in toward the cavity of the right ventricle). The initial diastolic change in septal position reflects the rapid initial flow of blood into the right ventricle while simultaneous inflow into the left ventricle is retarded by the narrowed mitral valve orifice. This creates a relative right ventricular volume overload during initial diastole which alters septal position and ventricular shape. (From Wayman A.E. et al: Mechanism of Paradoxical Early Diastolic Septal Motion in Patients with Mitral Stenosis. A Cross-Sectional Echocardiographic Study. *Amer J Cardiol* (in press))

produces a marked alteration in the position of the septum in space. These illustrations suggest that if one were to record a normal diastolic dimension of the left ventricle in a patient with a right ventricular volume overload the marked change in position of the septum would negate any attempt to relate this dimension to left ventricular volume since the shape of the ventricle no longer conforms to the geometric model on which this volume data is based.

A similar phenomenon occurs in patients with mitral stenosis. In these patients there is frequently a prominent abnormal or paradoxical motion of the interventricular septum occurring at the onset of ventricular diastole which corresponds to the maximal point of opening or E point of the mitral valve. In a study of 36 patients with mitral stenosis with a variety of associated lesions we observed that this marked paradoxical or diastolic motion of the



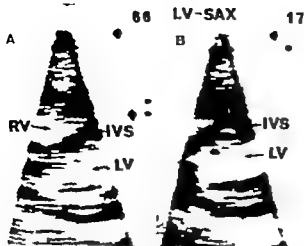


Fig 9 Short axis cross-sectional study of the left ventricle from a patient with marked right ventricular volume overload. In Panel A there is marked inward bending of the interventricular septum away from the right ventricle and inward toward the left ventricle such that the left ventricular cavity assumes a half moon appearance during diastole. Systolic contraction (Panel B) causes a return to the normal circular shape of

the left ventricle. This change in configuration of the ventricle from diastole to systole results in a marked anterior or paradoxical motion of the interventricular septum in space. (From Weyman A E et al. Mechanism of Abnormal Septal Motion in Patients with Right Ventricular Volume Overload. *Circulation* 54:179, 1976)

To examine this hypothesis the short axis configuration of the ventricle was examined in a group of patients with right ventricular volume overload and paradoxical septal motion (17). In this study it was noticed that when examined with the plane of the cross-sectional probe aligned parallel to the short axis of the left ventricular cavity the normal ventricle has a relatively circular configuration during diastole. During systole the walls of the ventricle move symmetrically inward toward the geometric center of the ventricle. During this contraction sequence the circular configuration of the ventricle is maintained (Fig 8). In contrast in patients with right ventricular volume overload the position of the septum during diastole was shifted away from the right ventricle and in toward the cavity of the left ventricle. This change in septal position altered the shape of the left ventricle during diastole from circular to flattened or half moon. During systole the rapid increase in left ventricular pressure forced the septum back in toward the right ventricle causing a return of the left ventricle to its normal circular configuration. This change in septal position and ventricular shape from diastole to systole produced a net anterior or paradoxical motion of the septum in space. Fig 9 is a recording from a patient with marked right ventricular volume overload. In the left hand panel recorded during diastole the interventricular septum curves away from the right ventricle and bulges inward toward the left ventricle. This changes the shape of the left ventricle from circular to kidney shape or half moon in configuration. In the systolic panel to the right the ventricle has returned to a normal circular configuration. This change in shape of the ventricle from systole to diastole

the left ventricle had returned to its normal shape and systolic contraction proceeded in a normal fashion

In order to determine the underlying causes of this phenomenon we divided these patients into those with and without a change in left ventricular diastolic shape. All hemodynamic parameters including cardiac output, left atrial pressure, pulmonary artery pressure, and left and right ventricular end diastolic pressures were similar for both groups. Only the mitral valve orifice size was significantly different between the two groups with those patients with an abnormal initial diastolic shape having smaller mitral valve areas. In addition, those patients with no abnormality of left ventricular diastolic shape had a far greater incidence of concomitant volume load on the left ventricle such as mitral insufficiency or aortic insufficiency. It was concluded from these data that the abnormality in diastolic shape in mitral stenosis was due to unequal filling of the two ventricles due to the stenotic lesion. At the onset of diastole the right ventricle fills rapidly due to the unimpaired tricuspid valve flow while left ventricular filling is restricted by the narrowed mitral valve orifice. This produces a relative right ventricular volume overload in initial diastole and thrusts the septum in towards the left ventricle. As diastole progresses, left ventricular filling is belatedly completed, thus equalizing the volumes of the ventricles and returning the septum gradually toward a more normal position. Fig 11 illustrates the relative rates of right and left ventricular filling and septal motion pattern in a patient with combined mitral stenosis and right ventricular volume overload.

These data suggest that there are a number of situations in which the shape of the ventricle may vary from normal during at least part of the cardiac cycle. It is also apparent that any method used to calculate ventricular volume or assess ventricular function which does not take into account these changes in ventricular shape will be subject to error.

#### CONCLUSION

This report therefore suggests that cross-sectional echocardiography is a reliable method for detecting changes in left ventricular shape in the ischemic and non-ischemic left ventricle. Abnormalities of shape produced by evaluation of the left ventricular wall in patients with ventricular aneurysms and invagination of the wall produced by change in left ventricular septal

septum was present on M-mode recording in 25 cases (18). Cross sectional studies in this group of patients revealed that coincident with the diastolic septal motion abnormality there was a change in left ventricular diastolic shape produced by a shift in septal position away from the right ventricle and in toward the left ventricle. Fig 10 is an example of the diastolic motion pattern of the interventricular septum during ventricular filling. As ventricular filling continued the septum gradually returned toward a more normal circular configuration so that by the onset of ventricular systole

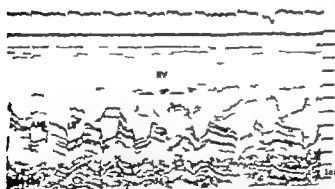
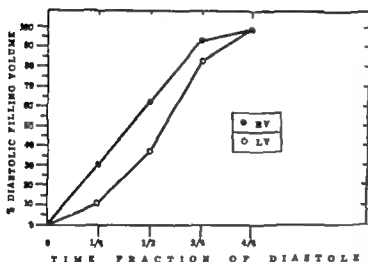


Fig 11 M-mode echocardiographic recording of the intraventricular septum and left ventricular cavity from a patient with combined mitral stenosis and right ventricular volume overload. In this figure the intraventricular septum moves paradoxically or anteriorly during systole and posteriorly during diastole. This abnormal initial diastolic septal motion again reflects the relative volume flows into the two ventricles in the initial portion of diastole. Because of the combined relative and absolute volume load on the right ventricle the septum fails to return to its normal position at end diastole and hence the shape of the ventricle remains abnormal. Ventricular systole therefore occurs with the ventricle still in an abnormal configuration with systolic contraction with systolic contraction back towards its normal configuration re-establishing

the normal shape of the ventricle and moves resulting in the paradoxical systolic motion of the interventricular septum. In the upper portion of this panel right and left ventricular filling expressed as a percentage of total filling of the ventricle are recorded for each of the four quarters of diastole. It is evident that due to obstruction to mitral valve inflow the filling of the left ventricle is significantly delayed in initial diastole relative to filling of the right ventricle. At end diastole both ventricles have filled to a hundred percent of their diastolic volume and therefore percent filling is equalled. Due to the associated right ventricular volume overload however the absolute volume of the right ventricle in this case would be greater than that of the left ventricle.

- 11 PETERSON J L JOHNSTON W HESSEL E A MURRAY J A Echocardiographic recognition of left ventricular aneurysm Amer Heart Journal 83 244 1972
- 12 CREMER R KERBER R E ABBODD F H Ventricular aneurysm Use of echocardiography J Clin Ultrasound 1 60 1973
- 13 TEICHOLZ L E COHEN M V SONNENBLICK E H GORLIN R Study of left ventricular geometry and function by B-scan ultrasonography in patients with and without asynergy New England J Med 291 1220 1974
- 14 YOSHITAKA J ONAKI T KATO H TANAKA K Ultrasonic diagnosis of ventricular aneurysm Circulation 49 30 1974
- 15 WEYMAN A E PESKOE S M WILLIAMS E S DILLON J C FEIGENBAUM H Detection of left ventricular aneurysms by cross section echocardiography Circulation 54 936 1976
- 16 ESTEVEZ C M WEYMAN A E FEIGENBAUM H Detection of a left ventricular diverticulum by cross sectional echocardiography Chest 69 544 1976
- 17 WEYMAN A E WARM L S FEIGENBAUM H DILLON J C Mechanism of abnormal septal motion in patients with right ventricular volume overload Circulation 54 179 1976
- 18 WEYMAN A E HEGER J J KRONIK G WARM L S DILLON J C FEIGENBAUM H Mechanism of paradoxical early diastolic septal motion in patients with mitral stenosis A cross sectional echocardiographic study Amer J Cardiol (in press)

position can be equally well evaluated. Much of the data relative to septal position although previously suspected could not be proven without the ability to view the short axis configuration of the left ventricle. This short axis view provides new and unique data which has heretofore been unobtainable by any invasive or noninvasive method. It is hoped that these improved methods of visualizing the dynamic geometry of the left ventricle will provide more accurate echocardiographic assessment of cardiac structure and function.

#### ACKNOWLEDGEMENT

*This work was supported in part by the Herman C. Krombert Ford and by Grants HL-06308 HL-05363 and HL-07182 from the National Heart Lung and Blood Institute of the National Institutes of Health U.S. Public Health Service and the American Heart Association Indiana Affiliate.*

#### REFERENCES

1. POMBO J F TROY B L RUSSELL R O Jr Left ventricular volume and ejection fraction by echocardiography *Circulation* 43:480 1971
2. FORTUIN N J HOOD W P Jr SHERMAN M E CRAIGE E Determination of left ventricular volume by ultrasound *Circulation* 44:575 1971
3. FORTUIN N J HOOD W P CRAIGE E Evaluation of left ventricular function by echocardiography *Circulation* 46:26 1972
4. COOPER R H O'Rourke R A KARLINER J S PETERSON K L LEOPOLD G R Comparison of ultrasound and cineangiographic measurements of the mean rate of circumferential fiber shortening in man *Circulation* 46:914 1972
5. FEIGENBAUM H Use of echocardiography in evaluating left ventricular function. Second World Congress on Ultrasonics in Medicine. Excerpta Medica 1974
6. FEIGENBAUM H Echocardiography. Second edition. Lea & Febiger Philadelphia 1976 p 317
7. TEICHHOLZ L E KREULEN T HERMAN M V GORLIN R Problems in echocardiographic volume determinations. Echocardiographic angiographic correlations in the presence or absence of asynergy. *Amer J Cardiol* 37:711 1976
8. BERMAN B MCGUIRE J Cardiac aneurysm. *Mer J Med* 8:480 1950
9. ABRAMS D L EDELSTEIN A LURIA M H Ventricular aneurysm. *Circulation* 27:164 1963
10. SCHIEHTER J HELLERSTEIN H K KATZ L N Aneurysm of the heart. correlative study of 102 proved cases. *Medicine* 33:1954

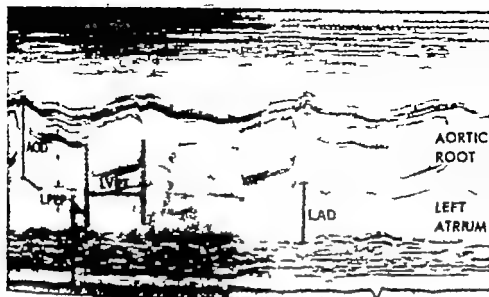


Fig 1. Electrocardiogram of the aortic root showing LPEP and LVET measurements  
 AOD = aortic root diameter LAD = left atrial dimension.

Since these estimations are just further mathematical elaborations of the  
 raw measurements and thus more prone to errors

Systolic time intervals have been measured from high speed recordings of  
 the echoes from the aortic leaflets (5 10) Left ventricular pre-ejection  
 period (LPEP) is measured from the beginning of the QRS-complex to the opening  
 of the leaflets and LVET from the opening to the closing of the leaf-  
 lets (fig 2) This is a more direct and in children an easier way of ob-  
 taining the systolic time intervals than the conventional method using  
 electrocardiogram phonocardiogram and external carotid pulse tracings

LVET varies strongly with heart rate (9) If the expected LVET for the  
 observed heart rate is calculated from the formula  $LVET = 372 - 52 \cdot 119 \times$   
 heart rate (unpublished material) and the actual LVET then is expressed as  
 percent of the expected LVET% the parameter is made independent of heart  
 rate (7) The quotient LPEP/LVET is another widely used parameter indepen-  
 dent of heart rate (1 3 4)

Measurements were compared to normal values obtained from a group of  
 51 children without heart disease (age 1 - 19 years)  $\Delta LVID = 34 \pm 8 \%$   
 Heart rate  $33 \pm 0.38$  circ/sec LPEP/LVET  $0.27 \pm 0.08$  LVET%  $100 \pm 8 \%$  (all  
 values given as mean  $\pm$  2 SD)

# ECHOCARDIOGRAPHIC ASSESSMENT OF LEFT VENTRICULAR FUNCTION DURING THE POSTOPERATIVE PERIOD IN CHILDREN OPERATED ON BECAUSE OF CONGENITAL HEART DISEASE

G BJÖRKHEM AND N -R LUNDSTRÖM

*From the Department of Pediatric Cardiology, University Hospital, Lund, Sweden*

During the last 18 months children operated on because of congenital heart disease in Lund have been followed by repeated echocardiographic examinations during the postoperative period to assess the changes induced in left ventricular function by the operation

As parameters of left ventricular function contractility indices and systolic time intervals have been used (2, 6, 8). The contractility indices are derived from measurements of the left ventricular internal dimensions in end-systole ( $LVID_s$ ) and in end-diastole ( $LVID_d$ ).  $LVID_d$  is measured at the beginning of the QRS-complex and  $LVID_s$  as the shortest distance between the left side of the septum and the endocardium of the posterior wall of the left ventricle in end-systole (fig 1). From these measurements shortening fraction or  $\Delta LVID$  is calculated as  $(LVID_d - LVID_s)/LVID_d$ . Mean velocity of circumferential fiber shortening (Mean Vcf) is derived from the same measurements and the left ventricular ejection time (LVET).  $Mean\ Vcf = (LVID_d - LVID_s)/LVID_d \times LVET$ . We have not attempted to calculate volumes and cardiac output

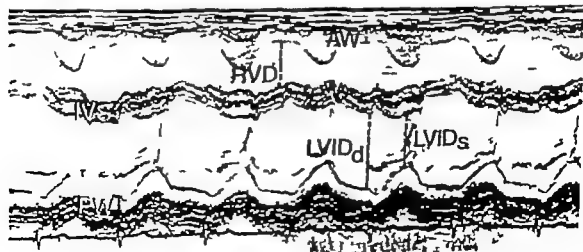


Fig 1 Echocardiogram of the left ventricle showing sites for measuring  $LVID_d$  and  $LVID_s$ . AW = anterior wall, RVD = right ventricular dimension, IVS = interventricular septum, PW = posterior wall of the left ventricle.

patients with AV-consumption (the complete form of endocardial cushion defect) showed a marked decrease in left ventricular function post-operatively. Patients who were operated on because of ASD, aortic stenosis (AS) and pulmonary stenosis (PS) that is with very short or no cardio-pulmonary by-pass showed normal function postoperatively. Two patients operated on because of coarctation of the aorta (CA) were included to evaluate if the thoracotomy as such would influence heart function but no decrease could be discerned. The patients with aortic stenosis usually had a high  $\Delta$ LVID preoperatively which actually increased in the immediate postoperative period and then slowly normalized.

Fig 3 shows the changes in left ventricular function postoperatively in an 8-year-old boy operated on with correction of Fallot's anomaly and closing of a Waterston shunt. Preoperative function is normal and immediately after the operation  $\Delta$ LVID, Mean Vcf and LVET% decreases and

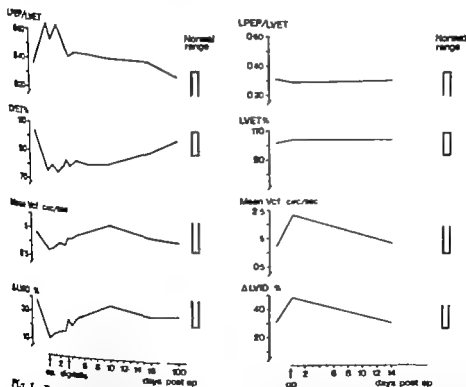


Fig 3: Parameters of left ventricular function (LPEP/LVET, LVET%, Mean Vcf,  $\Delta$ LVID) pre- and postoperatively in an 8-year-old boy operated on with correction of Fallot's anomaly and closure of a Waterston shunt.

Fig 4: Parameters of left ventricular function (LPEP/LVET, LVET%, Mean Vcf,  $\Delta$ LVID) pre- and postoperatively in a 7-year-old boy operated on with correction of a coarctation of the aorta.



TABLE 1: Clinical material - diagnosis number of patients and postoperative left ventricular function

DIAGNOSIS	NUMBER	POSTOPERATIVE LV-FUNCTION
Fallot + Waterston	6	↓
Fallot	8	↓
ASD + VSD	1	↓
VSD + PULM BANDING	9	↓\
VSD + PS	5	↓
VSD	5	\
ASD + PS	1	→
ASD	14	→
MS	1	↓
AV - commune	2	↓
AS	6	→
PS	2	→
CA	2	→

The children have been examined preoperatively and on the day of the operation or the following day. After that examinations have been done daily for a period or with longer intervals depending on the cardiac status and the speed of recuperation.

So far 62 children have been followed. Table I shows the number of patients in each group and also gives a rough estimate of the decrease in left ventricular function postoperatively for each group. Patients undergoing more extensive operations such as correction of Fallot's anomaly and closing of a Waterston shunt, correction of Fallot's anomaly without previous shunt closing of an atrial septal defect (ASD) + a ventricular septal defect (VSD), closing of a VSD and debanding of the pulmonary artery all showed a marked decrease in left ventricular function. In the group operated on with closing of a VSD and debanding there is a less marked decrease in left ventricular function in those patients where the band could be removed without damaging the pulmonary artery and the operation thus was shorter and less complicated. Patients operated on with closure of a VSD or closure of a VSD and removal of an infundibular pulmonary stenosis (PS) showed intermediate decrease in left ventricular function. The patients with complicated operations as one boy reoperated upon because of a mitral stenosis (MS) and two

here seem to be a close correlation between the degree of post-operative decrease in left ventricular function and the extent of the operation especially concerning cardio-pulmonary by-pass time aorta clamping time and problems encountered during the operation but this has to be evaluated further

For several reasons we have not followed many patients who have died soon after the operation. One patient who was operated on with correction of Fallot's anomaly died on the second post-operative day and that patient had a LVETS of 60% immediately post-operatively. The same low value was recorded in a patient operated on because of VSD and pulmonary hypertension who also died on the second post-operative day. Values of LVETS as low as 60% thus seem to indicate a very grave prognosis. Included in the group of patients with Fallot is one girl who initially went down in LVETS to 60%, the value remaining there for about one week but then decreasing to 50% before the patient died in complications to the operation including bacterial pericarditis.

As was mentioned before pathological septal movement can often be seen postoperatively also in patients who had normal septal movement before the operation. Often the movement pattern returns to normal within the first post-operative week but the septum may also remain immobile. On the third or fourth post-operative day an echo-free space is often found behind the heart probably representing fluid in the opened pericardium. This is seen in patients progressing normally and without signs of post-cardiotomy syndrome. The echo-free space usually disappears within ten days. If on the other hand a similar echo-free space is noticed on the day of the operation or early the next day it usually represents an on-going hemorrhage and we have seen several cases where re-operation was necessary. The size of the left atrium usually diminished directly postoperatively after closing of a VSD and if the size increases again it is often the first sign of a disrupted patch.

Thus the post-operative echocardiographic examination can be a value in detecting complications apart from the estimation of left ventricular function. The degree of postoperative decrease in left ventricular function is an indicator of how well the myocardium withstood the operation and can be used to evaluate different operative techniques and maybe to predict the outcome.

LPEP/LVET increases as would be expected when myocardial function is impaired. On the third day the boy was digitalized and when examined 1 hour after the initial parenteral dose of digitalis left ventricular function actually seemed to have improved. For comparison fig 4 shows left ventricular function pre and postoperatively in a 7-year-old boy operated on with correction of a coarctation of the aorta- here no decrease in left ventricular function could be discerned.

On the parameters used to assess left ventricular function Mean Vcf seems to be the least sensitive with its large normal range. The other parameters are influenced about equally but LPEP/LVET is the one to normalize last usually over weeks to months. During the immediate postoperative period LVET% is the parameter that is most convenient to use when comparing different groups of patients since  $\Delta$  LVID and Mean Vcf can be unreliable if some patients in a group have inverse septal movement postoperatively and LPEP/LVET can be deranged due to the use of a pacemaker during the first postoperative days.

TABLE II: Range of LVET% in the immediate postoperative period for different groups of patients

	POSTOP LVET %
	range
FALLOT + WATERSTON	64 - 84 %
FALLOT	66 - 90 %
VSD + PULM BANDING	68 - 83 %
OTHER DIAGNOSIS	70 - normal

Table II gives the range of LVET% in the immediate postoperative period in the different groups. Only patients surviving the first postoperative week are included. In the group operated on with correction of Fallot's anomaly and closing of a Waterston shunt LVET% decreased to 64% at the most and to 84% in the patient who withstood the operation the best. Among the patients with Fallot's anomaly without previous shunt there is one patient who did not decrease in LVET% to more than 90% which is very close to the lower normal limit of 92%. This was a girl who withstood the operation extremely well in all respects. The patient coming closest to her had a lowest LVET% of 85%.

# PULMONARY VALVE MOTION IN VALVULAR PULMONARY

## STENOSIS IN CHILDHOOD

C. KEY AND J. M. LABLANCHE

*Des Services de Cardiologie Infantile Hôpital Calmette Lille France*

### SUMMARY:

Echocardiography tracings of the pulmonary valve was recorded in 14 patients with pulmonic stenosis (PS) ranging in ages from 6 to 14 years (average 10 years). 11 patients had an isolated PS and 3 had a PS associated with atrial septal defect.

In 2 patients with mild PS (gradient 15 mm Hg) the depth of the a wave was normal: 3 and 4 mm.

In 14 patients with moderate or severe PS (gradient 40 mm to 204 mm Hg) the maximal depth of the a wave was less than 6 mm in 2 patients and more than 6 mm in 12 patients (range 7 to 15 mm average 10 mm). The motion of both anterior and posterior pulmonary valve leaflets was well recorded in 3 patients with severe PS. The a wave showed a posterior motion of the posterior leaflets and an anterior motion of the anterior leaflet. This motion is due to the premature pulmonary valve opening.

---

Since the initial observations of pulmonary valve by echocardiography (3) the posterior motion after the atrial contraction (a wave) has been well described. The absence of a wave in severe pulmonary hypertension and the exaggerated leaflet motion in pulmonary stenosis has previously been reported (5, 10, 13). The purpose of this report is to evaluate the pulmonary valve motion following the atrial contraction in children with valvular pulmonary stenosis.

# REFERENCES

- 1 ANDRIAS C W DEANE L V BRONSTEIN A B and GAASCH W H  
Relative sensitivity of systolic time intervals & echocardiography in  
the assessment of a positive inotropic intervention in normal subjects  
Circulation 54 suppl II 59 1976
- 2 COOPER R KARLINER J S O ROURKE R A PETERSON K L and LEOPOLD  
D Ultrasound determination of mean fiber shortening rate in man  
Amer J of Cardiol 29 257 1972
- 3 GUTGESELL H P PAQUET M DUFF D F and McNAMARA D G. Left ventri-  
cular function in normal children Effects of age and heart rate  
Circulation 51 + 52 suppl II 9 1975
- 4 GUTGESELL H P PAQUET M DUFF, D F and McNAMARA D G. Left ventri-  
cular function in children with congestive cardiomyopathy. Pediatric  
Research 10 313 1976
- 5 HIRSCHFELD S MEYER R SCHWARTZ D C KORFHAGEN J and KAPLAN S  
Measurement of right and left ventricular systolic time intervals by  
echocardiography Circulation 51 304 1975
- 6 LEWIN R P LEIGHTON R F FORESTER W F and WEISSLER A M Systolic  
time intervals IN Noninvasive Cardiology PP 301 368 Editor A M  
Weissler Grune and Stratton New York - London
- 7 MEINERS S. Messmethoden zur Analyse der Herz - und Kreislaufdynamik  
pp 84 - 90 Freiburger Colloquium München 1958
- 8 SAHN D J ALLEN H D and GOLDBERG S J The comparative utility  
of echocardiographic indices for the detection of depressed left ventri-  
cular function in children Amer J of Cardiol 37 168 1976
- 9 SPITAELS S ARBOGAST R FOURON J C and DAVIGNON A The influence  
of heart rate and age on the systolic and diastolic time intervals in  
children Circulation 49 1107 1974
- 10 VREDEVOE L A CREEKMORE S P and SCHILLER N B The measurement of  
systolic time intervals by echocardiography J of clinical Ultrasound  
2 99 1974

# PULMONARY VALVE MOTION IN VALVULAR PULMONARY STENOSIS IN CHILDHOOD

R. REY AND J. M. LABLANCHE

*From Service de Cardiologie I infantile Hôpital Calmette Lille France*

## SUMMARY:

Echocardiography tracings of the pulmonary valve was recorded in 18 patients with pulmonic stenosis (PS) ranging in ages from 6 to 14 years (average 10 years). 11 patients had an isolated PS and 5 had a PS associated with atrial septal defect.

In 2 patients with mild PS (gradient 15 mm Hg) the depth of the a wave was normal: 3 and 4 mm.

In 14 patients with moderate or severe PS (gradient 40 mm to 200 mm Hg) the maximal depth of the a wave was less than 6 mm in 2 patients and more than 6 mm in 12 patients (range 7 to 15 mm average 10 mm). The motion of both anterior and posterior pulmonary valve leaflets was well recorded in 3 patients with severe PS. The a wave showed a posterior motion of the posterior leaflets and an anterior motion of the anterior leaflet. This motion is due to the premature pulmonary valve opening.

---

Since the initial observations of pulmonary valve by echocardiography (3) the posterior motion after the atrial contraction (a wave) has been well described. The absence of a wave in severe pulmonary hypertension and the exaggerated leaflet motion in pulmonary stenosis has previously been reported (5, 10, 13). The purpose of this report is to evaluate the pulmonary valve motion following the atrial contraction in children with valvular pulmonary stenosis.

## MATERIAL AND METHODS

The clinical material consisted of 3 groups of patients

Group I was composed of 16 patients with valvular pulmonary stenosis documented by cardiac catheterization studies. Their ages ranged from 6 to 15 years, the average being 10 years. There were 8 males and 8 females. Eleven patients had isolated valvular pulmonary stenosis, 5 had pulmonary stenosis and ASD with a moderate left to right shunt ( $QP/QS < 2$ ). At catheterization the systolic pressure gradient between the pulmonary artery and the right ventricle was mild in 2 cases (15 mm Hg), moderate in 13 cases (gradient 40 to 90 mmHg), severe in one case (gradient 200 mm Hg).

The echocardiographic patterns seen in patients of the first group were compared with those in the two other groups.

Group II 20 normal patients, age 5 to 15 years. These patients did not undergo cardiac catheterization but clinical examination, ECG and X ray were normal.

Group III 20 patients, age 6 to 15 years with isolated ASD documented by cardiac catheterization.

All ultrasonic examinations were carried out using a commercially available echograph (EchocardioVisor, Organon Teknika).

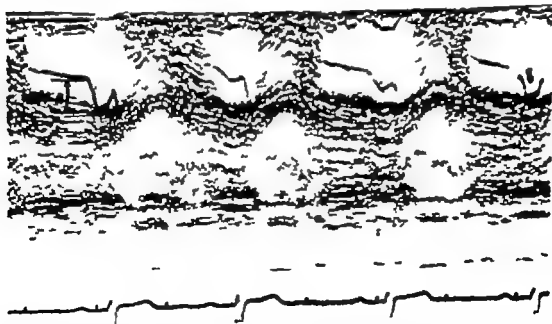


Fig 1 Child, age 15 years, with moderate pulmonary stenosis (gradient 50 mm Hg). Posterior pulmonary leaflet recording. During the inspiration in the first and fourth complex from the left the "a" wave depth is 15 mm. The second complex was recorded during expiration and the "a" wave depth was normal.



Fig 2: Child age 14 years with moderate pulmonary stenosis (gradient 40 mm Hg) Anterior and posterior pulmonary leaflets recording. The anterior pulmonary valve leaflet moves anteriorly after atrial systole and posterior pulmonary valve leaflet moves posteriorly

A 5 MHz unfocused transducer was used to record the pulmonary valve echo. Strip chart recordings were obtained with a Honeywell recorder.

Pulmonary valve echocardiograms were obtained by the method previously described by Graziak and al (3). The aortic root is identified and from this position the ultrasonic beam was then angled superiorly and laterally toward the left shoulder. The depth of the a wave increased with inspiration. Therefore continuous pulmonary valve recording was performed during one respiration cycle in all patients. Only maximal a wave depth was considered (Fig 1).

## RESULTS

Group 1: The a wave was 3 to 15 mm (average 9 mm). In the 2 cases with mild valvular pulmonary stenosis (gradient 18 mm Hg) the a wave was 3 and 4 mm. In the 13 cases with moderate stenosis (gradient 40 to 90 mm Hg) the a wave ranged 4 to 15 mm (average 10 mm). There was no difference about the a wave between the patients with isolated pulmonary stenosis and the patients with pulmonary stenosis and ASD. In 8 patients with isolated pulmonary stenosis the a wave averaged 10.4 mm (range 4 to 15 mm); in the 5 patients with pulmonary stenosis and ASD the a wave averaged 9.6 mm (range 5 to 11 mm). In the patient with severe pulmonary stenosis (gradient 200 mm Hg) the a wave was only 7 mm. Both anterior and posterior



leaflets were recorded in 3 cases with moderate stenosis (fig 2) After atrial contraction the anterior leaflet moved anteriorly and the posterior one moved posteriorly

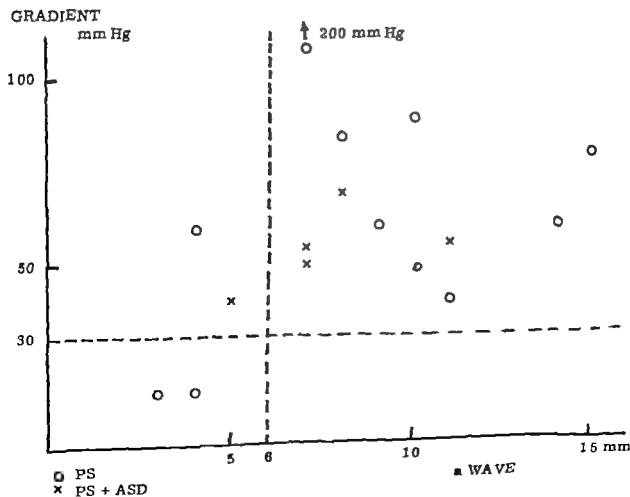
Group II and III During inspiration and expiration the maximal a wave was equal or inferior to 6 mm

### DISCUSSION

The pulmonary valve is more easily located and recorded in children than in adults and more easily recorded if the pulmonary artery is dilated The pulmonic valve was well recorded in 16 of our 18 cases of valvular pulmonary stenosis

In 3 patients the anterior leaflet motion was recorded This motion is easily recorded in the newborns and in patients with pulmonary hypertension

TABLE I



or with important left to right shunt (4-10). On the other hand this anterior leaflet motion is rarely recorded in the other cardiac malformations. In our three observations the transducer was in the second left interspace position so the ultrasonic beam is more perpendicular to the pulmonary artery and therefore both the anterior and posterior pulmonary leaflets are more easily recorded than in the third or fourth interspace position. In addition the distal a-f slope the magnitude of the a wave seems less important to the second interspace than in the third one because the ultrasonic beam is more perpendicular.

In normal adults the maximal a wave depth recorded by Weyman is 7 mm (9). Our study shows a maximal a wave magnitude of 6 mm in children.

There is no correlation between the a wave depth and the systolic pressure gradient between the pulmonary artery and the right ventricle (table I). In one case with severe pulmonary stenosis (gradient 200 mm Hg) the a wave is only 7 mm and in 2 of 13 cases of moderate stenosis the a wave is normal but in the mild stenosis the a wave depth is within the normal range as Weyman has previously reported (9).

In the normal subjects the anterior and posterior pulmonary valve leaflets move after the onset of ventricular systole. The right ventricular pressure is superior to the pulmonary artery pressure. In the patients with pulmonary stenosis the a wave is a premature pulmonary valve opening following atrial contraction. This fact is demonstrated by hemodynamic studies (2, 7). In our study catheterization was not performed simultaneously with the echocardiographic examination. However right ventricular pressure equals or exceeds pulmonary artery pressure at the peak of a wave causing the pulmonary valve to open (7). In echocardiographic tracings motion of the anterior and posterior pulmonary valve leaflets is symmetrical at the moment of the a wave in 3 patients.

The anterior pulmonary valve leaflet is separated from the posterior leaflet after atrial systole and indicates that the large a wave reflects opening or doming of the valve. However the maximal amplitude of this leaflet separation after atrial systole is the same as after ventricular contraction. So this fact indicates that the large a wave is an opening of the valve and not doming.

Pulmonary valve opening occurs during ventricular systole in the normal subject. But an increase in right ventricular end-diastolic pressure to a level equalling or exceeding pulmonary artery pressure will produce opening of the pulmonary valve. This right ventricular end diastolic pressure increase occurs in certain situations: valvular pulmonary stenosis particularly during inspiration, decrease of right ventricular compliance.

In Tetralogy of Fallot, premature pulmonary valve opening has been already described at catheterization (1) but not at echocardiography because the pulmonary valve is rarely recorded.

Premature pulmonary valve opening can be independent of atrial systole (7) but it is very rare. This premature pulmonary valve opening was noted in constrictive pericarditis, Loeffler's endocarditis, Ebstein's anomaly with tricuspid regurgitation, tricuspid regurgitation following tricuspid valvelectomy, pulmonary regurgitation accompanied by atrial septal defect and Valsalva aneurysm rupture into the right atrium (2, 7, 12). Premature opening of the aortic valve in late diastole, demonstrated by echocardiography in a patient with severe aortic regurgitation (6, 8) was due to a pressure equalization between the left ventricle and aorta.

We conclude that an augmented  $a$  wave in patients with moderate and severe pulmonary stenosis does reflect premature opening of pulmonary valve. But this premature opening occurs in other situations and is not specific for pulmonary stenosis. In children with valvular pulmonary stenosis, the  $a$  wave is very often increased when the gradient is superior to 40 mm Hg (12 of 14 children in our study).

## REFERENCES

1. CHAMBERS R J, BECK W, SCHRIRE V. Complete functional systolic obstruction of the right ventricular outflow in the Tetralogy of Fallot. *American Heart J* 80: 677, 1970.
2. FRENCH J W, BAUM D, POPP R L. Echocardiographic findings in Uhl's Anomaly. *American Heart J* 36: 349, 1975.
3. GRAMIAK R, NANDA N C, SHAH P M. Echocardiographic Detection of the Pulmonary Valve. *Radiology* 102: 153, 1972.
4. LESBRE J P, BERNASCONI P, REY C, LABLANCHE J M. Atlas d'Echocardiographie. *Substantia* 110, 1976.

5. KADA H C, GRAHIAK R, ROBINSON T I, SHAH P M Echocardiographic Evaluation of Pulmonary Hypertension Circulation 50 575 1974
6. PAGE A, LAYTON E Premature opening of aortic valve in severe aortic regurgitation British Heart J 37 1101 1975
7. WALK L S, WEYMAN A E, DILLON J C, FEIGENBAUM H Premature pulmonary valve opening Circulation 55 128 1977
8. MEYER W F, WILSON C S, ROURKE T, CAYDILL C E Mid-diastolic aortic Valve Opening in Severe Acute Aortic Regurgitation Circulation 55:145 1977
9. WEYMAN A E, DILLON J C, FEIGENBAUM H, CHANG S Echocardiographic Patterns of Pulmonary Valve Motion in Valvular Pulmonary Stenosis American J Cardiol 34 644 1974
10. WEYMAN A E, DILLON J C, FEIGENBAUM H, CHANG S Echocardiographic Patterns of Pulmonic Valve Motion with Pulmonary Hypertension Circulation 50 905 1974
11. WEYMAN A E, DILLON J C, FEIGENBAUM H, CHANG S Echocardiographic Differentiation of Infundibular from Valvular Pulmonary Stenosis American J Cardiol 36 21 1975
12. WEYMAN A E, DILLON J C, FEIGENBAUM H, CHANG S Premature Pulmonic Valve Opening Following Sinus of Valsalva Aneurysm Rupture into the Right Atrium Circulation 51 556 1975
13. WEYMAN A E, DILLON J C, FEIGENBAUM H, CHANG S Pulmonary Valve echo motion in pulmonary regurgitation British Heart J 37 1184 1975

# ECHOCARDIOGRAPHY IN THE DIAGNOSIS OF SUBAORTIC STENOSIS

N -R LUNDSTRÖM

*From Department of Pediatric Cardiology University Hospital Lund  
Sweden*

During the routine echocardiographic examination of the heart using the M-mode scanning the outflow tract of the left ventricle is easily examined. In the view seen by the ultrasound beam during this M-mode scanning the anterior border of the outflow tract consists of the interventricular septum and the posterior border of the anterior mitral leaflet (Fig 1). As a measurement of the width of the outflow tract (LVOT<sub>d</sub>) we have taken the shortest distance between the left side of the interventricular septum and the anterior mitral leaflet in end-diastole as indicated on Fig 1.

The patient material studied consists of all patients with a subaortic stenosis examined with echocardiography. The patients with a hypertrophic obstructive cardiomyopathy are excluded. The material comprises 13 patients aged 2 months to 13 years (mean and median age 7 years). Five of the

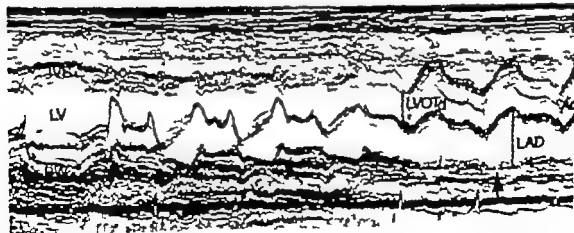


Fig 1 Echocardiogram obtained by M-mode scanning along the longaxis of the left ventricle (LV) up to the aortic root (Ao) in a child without heart disease. The site of measurement of the left ventricular outflow tract dimension in end-diastole (LVOT<sub>d</sub>) is indicated.

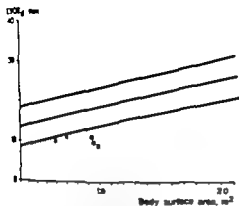


Fig 2. Diagram showing the left ventricular outflow tract dimension in end-diastole (LVOTD) in the patients with subaortic stenosis in relation to the normal values. The lines indicate the mean  $\pm$  2 SD. The patients with subaortic membrane are indicated by a circle, the patients with a fibromuscular collar-like stenosis by a square and the patient with the obstruction caused by an abnormal papillary muscle by the triangle.

Patients had a subaortic thin membrane, seven patients a longer fibromuscular collar-like stenosis and in one patient the stenosis was caused by a single abnormally placed papillary muscle of the mitral valve. The diagnosis was in all patients based on heart catheterization and angiography. The diagnosis was further verified at operation in eight patients and at autopsy in the patient with the abnormal papillary muscle causing the stenosis.

It has previously been shown (Popp et al 1974) that an echo from a subaortic membrane can be obtained by echocardiography. Such an echo could not be obtained in any of our five patients with a membranous subaortic stenosis despite prior knowledge of the diagnosis in four of them. The possibility of obtaining echoes from such a membrane depends on the spatial orientation of the membrane in relation to the ultrasonic beam.

The most constant abnormal finding in our patients was a narrow outflow tract of the left ventricle. All patients with a fibromuscular collar-like stenosis had an outflow tract of the left ventricle more narrow than normal (Fig 2). Four of the five patients with a membranous subaortic stenosis also had an outflow tract more narrow than normal (Fig 2). The most narrow outflow tract was found in the two months old boy with a stenosis caused by an abnormal papillary muscle (Fig 2). A M-mode scan from the left ventricle up to the aortic root from this patient is seen in Fig 3. The outflow tract of the left ventricle can be seen to be extremely narrow.

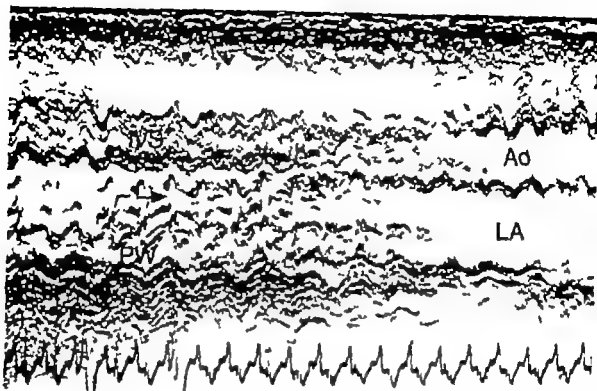


Fig 3 Echocardiogram obtained by M-mode scanning from the left ventricle up to the aorta (Ao) in the patient with a subaortic stenosis caused by an abnormal papillary muscle. The interventricular septum (IVS) is thickened. The outflow tract of the left ventricle (oblique arrow) is extremely narrow compared to the width of the aorta root. The horizontal arrow points to the echoes from the mitral valve.

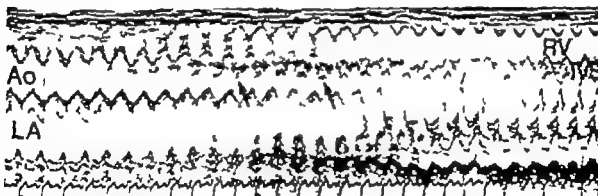


Fig 4 Echocardiogram obtained by M-mode scanning from the aorta (Ao) to the left ventricle in a patient with a subaortic stenosis of the fibromuscular collar-like type. The oblique arrow point to the narrow outflow tract of the left ventricle. The length of this stenosis cannot be estimated by this method.

In a M-mode scan along the outflow tract of the left ventricle the length of a subaortic stenosis cannot be determined since the length seen on such a recording also depends on the speed with which the scanning is performed (Fig 4). Information about the length of the stenosis can be obtained by

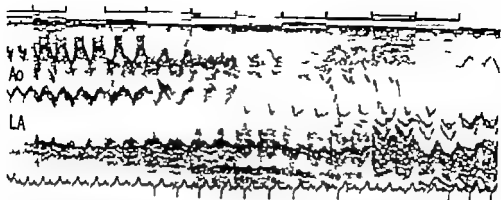


Fig 6 Echocardiogram obtained by single-element echocardiography by use of a multi-element transducer on the same patient as in Fig 4 and with the transducer placed along the long-axis of the left ventricle. The small markings on the top of the recording indicate the border between the echocardiograms obtained from each individual line on the multi-element transducer. With the transducer used for this examination the distance between the level from which two adjacent short echocardiograms are obtained is 4 mm. It can thus be shown that this subaortic stenosis is short.

two-dimensional echocardiography or by single-element echocardiography by use of the multi-element transducer (Lundström and Hansson 1977) as shown in Fig 5 (the same patient as in Fig 4).

It has been described previously that an abnormal motion of the echoes from the aortic leaflets can be seen in patients with a subaortic stenosis (Davis et al 1974). Such an abnormal motion of at least one of the aortic leaflet echoes could be seen in all the nine patients where echocardiogram from the aortic root was of adequate quality to study the motion of the aortic leaflet echoes.

In summary it seems possible to identify a localized subaortic stenosis by M-mode echocardiography in most patients. The most important echocardiographic finding has been the demonstration of a narrow outflow tract of the left ventricle. Identification of a subaortic thin membrane seems more unreliable. The length of a subaortic stenosis cannot be provided by M-mode echocardiography but can be obtained by two-dimensional echocardiography.

#### REFERENCES

1. DAVIS R H, FEIGENBAUM H, CHANG S, KONECKE L L and DILLON J C. Echocardiographic manifestations of discrete subaortic stenosis. *Amer J Cardiol* 33:227 1974.
2. LUNDSTRÖM R R and HANSSON R. Single-element echocardiography by multi-element automatic sequential line-selection. In this issue.
3. POPP R L, SILVERMAN J F, FRENCH J W, STINTON E B and HARRISON D C. Echocardiographic findings in discrete subvalvular aortic stenosis. *Circulation* 49:226 1974.



## TWO-DIMENSIONAL ECHOCARDIOGRAPHY IN ATRIOVENTRICULAR CANAL MALFORMATION A DIAGNOSTIC APPROACH

H A Y DRAULANS-NOË P J VOOGD C M LIGTVOET J RIDDER  
AND A C G WENINK

*From the Departments of Pediatric Cardiology, Cardiology and Anatomy, University Hospital, Leiden, The Netherlands and the Interuniversity Cardiology Institute, Rotterdam, The Netherlands*

### SUMMARY

Two-dimensional echocardiographic studies were performed in 20 children with various forms of atrio-ventricular canal malformation. Both sagittal and transverse cross-sections were evaluated. The most typical finding in all patients was the visualization of the cleft anterior mitral leaflet (AML) represented by a diastolic break of AML echoes in the sagittal cross-section. - In cases where the AML is attached to the interventricular septum, varying degrees of left ventricular outflow tract narrowing and elongation were observed.

In the transverse cross-section mitral-tricuspid alignment could be observed at the level of the aortic root. The ventricular septal defect in complete AVC was visualized as an echo-free space between the common anterior leaflet and the interventricular septum.

---

The purpose of this study is to assess the value of multiple-crystal two dimensional echocardiography in children with various forms of atrioventricular canal malformation (AVC). In this report we describe features common to all patients, including visualization of the characteristic cleft in the anterior mitral leaflet (AML) as well as specific findings in children with complete AVC. The importance of adjusted transducer position is stressed and the advantages of continuously focussed multiscan system

TABLE 1

## PATIENT MATERIAL

## ATRIOVENTRICULAR CANAL MALFORMATION (20 CHILDREN)

GROUP I	INCOMPLETE AVC	8 children
	ASD I	7 children
	VSD (of the AVC type)	1 child
GROUP II	ASD I + VSD no PH	5 children (1 x Down s syndrome)
GROUP III	COMPLETE AVC with PH at systemic level	7 children (6 x Down s syndrome)

ABBREVIATIONS AVC = atrioventricular canal ASD I ostium primum atrial septal defect VSD ventricular septal defect PH = pulmonary hypertension

## PATIENT AND METHODS

Twenty children with AVC malformation (table 1) ranging in age from 2 to 14 years (average 8 years) were examined with a prototype multiple crystal continuously focussed linear array echocardiographic system developed in the experimental echocardiographic laboratory of the Thoracic Center Rotterdam (2,3).

Eight patients had incomplete forms of AVC malformation (group I table 1) with an atrial septal defect of the primum type (ASD I) in 7 patients and a ventricular septal defect (VSD) of the AVC type in 1 patient. Five patients had an ASD I with additional VSD but without significant pulmonary hypertension.



Fig 1 Schematic representation of the abnormal motion pattern of the left AML in AVC. Sagittal cross-section atrial septal defect of the primum type I distals the lower mobile part of the superior (S) segment of the AML moves anteriorly and upwards into the left ventricular outflow tract (LVOT) while the inferior (I) segment moves in the opposite direction. The upper part of the superior segment is less mobile due to its chordal attachments to the interventricular septum. It forms the posterior border of the elongated narrow LVOT. RV=right ventricle, LV=left ventricle, LA=left atrium.

## TWO-DIMENSIONAL ECHOCARDIOGRAPHY IN ATRIOVENTRICULAR CANAL MALFORMATION A DIAGNOSTIC APPROACH

H A Y DRAULANS-NOË P J VOOGD C M LIGTVOET J RIDDER  
AND A C G WENINK

*From the Departments of Pediatric Cardiology Cardiology and Anatomy University Hospital Leiden The Netherlands and the Interuniversity Cardiology Institute Rotterdam The Netherlands*

### SUMMARY

Two-dimensional echocardiographic studies were performed in 20 children with various forms of atrio-ventricular canal malformation Both sagittal and transverse cross-sections were evaluated The most typical finding in all patients was the visualization of the cleft anterior mitral leaflet (AML) represented by a diastolic break of AML echoes in the sagittal cross-section - In cases where the AML is attached to the interventricular septum varying degrees of left ventricular outflow tract narrowing and elongation were observed

In the transverse cross-section mitral-tricuspid alignment could be observed at the level of the aortic root The ventricular septal defect in complete AVC was visualized as an echo-free space between the common anterior leaflet and the interventricular septum

---

The purpose of this study is to assess the value of multiple-crystal two dimensional echocardiography in children with various forms of atrioventricular canal malformation (AVC) In this report we describe features common to all patients including visualization of the characteristic cleft in the anterior mitral leaflet (AML) as well as specific findings in children with complete AVC The importance of adjusted transducer position is stressed and the advantages of continuously focussed multiscan system

(78) (group II) So far one of these patients proved to have a complete APC with central VSD at operation. Seven patients had a complete AVC with AI at systemic level (group III) and Down's syndrome in 6 of them.

Each patient had the typical clinical and electrocardiographic findings of APC malformation which could be confirmed by left ventricular angiocardiography in 18 children.

A 1.12 mHz 51 element transducer was used in all patients producing images at a frame rate of 80/sec and displaying a total of 80 lines of the oscilloscope. The real time images viewed on the oscilloscope were stored on video tape (4) and copied on 16 mm motion film and/or polaroid photographs.

Sagittal and transverse cardiac cross sections were evaluated with the transducer placed respectively vertically along the left sternal border and horizontally in the fourth intercostal space with the superior crystal to the right.

## RESULTS

### SAGITTAL CROSS-SECTION

In patients with the AML attached to the interventricular septum (IVS) (group I and III) the AML seemed to consist of an immobile upper part (fig 1) forming the posterior border of the left ventricular outflow tract (LVOT) and a mobile lower part. In systole the immobile upper part failed to move to a normal position posterior to the aortic root (fig 2). Most cha-

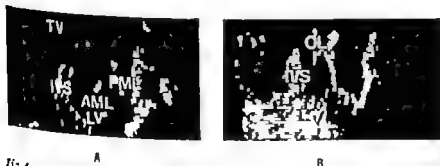


Fig 1 Sagittal transverse cross-section at the level of the left ventricular outflow tract

1. Atrial septal defect of the secundum type normal mitral - tricuspid discontinuity is well visualized.
2. Complete APC showing mitral - tricuspid alignment. The ventricular septal defect is visualized as an echogenic space between the common anterior leaflet (CL) and the IVS - tricuspid valve.

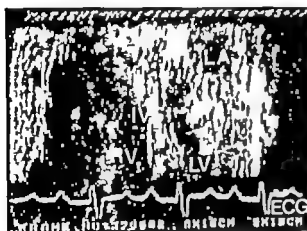


A

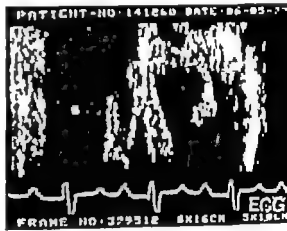


B

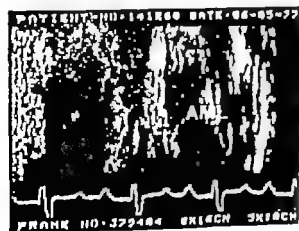
Fig 2 Normal sagittal cross-section (polaroid photo) A = diastole B = systole The anterior mitral leaflet (AML) moves anteriorly towards the inter-ventricular septum (IVS) in diastole Systolic valve closure brings the AML to a position posterior to the root of the aorta RV=right ventricle LV=left ventricle LA=left atrium PML=posterior mitral valve



A



B



C

Fig 3 Sagittal cross-section atrial septal defect of the primum type  
A Early diastole a break in anterior mitral leaflet (AML) echoes appears This is caused by the mobile part of superior segment (S) of the AML moving anteriorly and upwards into the left ventricular outflow tract while the inferior segment (I) moves in the opposite direction This diastolic break represents the cleft AML  
B End-diastole  
C Systole Both segments of the AML have approximated again the cleft is not visible Systolic posterior motion of the AML is reduced

## DISCUSSION

Two-dimensional echocardiographic studies in patients with AVC malformation have been reported in the literature (1-7) including multiple crystal evaluation (5). These studies however are limited and we feel that better understanding of the anatomy and recent improvement in technique (3) has improved our possibilities for correct interpretation of the echocardiographic features in these patients.

In AVC malformation the AML is not only malformed (being cleft) but also mispositioned due to absence of the atrioventricular septum (fig 5) and shows an abnormal motion pattern (fig 5 and 6). Both parts of the cleft AML are situated perpendicular to the IVS rather than parallel to it as in normally the case. Its plane of motion is parallel to the IVS. In order to visualize the abnormally placed AML and its motion pattern we adjusted our transducer position accordingly into a rather vertical plane of section. In this position the echo beam will reach both segments of the AML and the diastolic cleft in between. The PLM will hardly be visualized as it is not reached by the echo beam.

Valvular septal apposition and reduced posterior motion of the AML in the sagittal cross-section are well-established features in patients with AVC malformation both in M-mode scanning and two-dimensional techniques (5). Anterior displacement and reduced systolic posterior motion of the fixed part of the AML may result in varying degrees of the LVOT elongation and narrowing. We feel that this may prove to give us some information on the severity of the anomaly as has been described for the shape of the LVOT on left ventricular angiocardiology (6).

The most characteristic observation however was the visualization of a diastolic "break" in AML echoes in all our patients regardless of the type of the anomaly. So far we have not encountered this feature in normal subjects nor in approximately 40 patients with various forms of congenital or acquired heart disease studied in the same period with the same technique. We feel that this diastolic "break" in AML echoes represents the diastolic cleft of the AML. Review of the anatomy confirms this assumption.

Transverse cardiac cross section with the echo-beam directed towards the aortic root normally shows approximation of the tip of the anterior tricuspid valve echo to the medial end of the IVS during systole separating from it during diastole. Normal septal aortic continuity can also be observed at

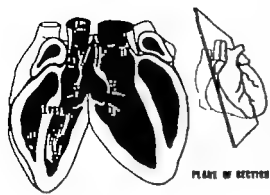


Fig 6 Anatomical drawing illustrating the abnormal mitral valve in AVC (i.e. atrial septal defect of the primum type) in a sagittal cross-section. The anterior leaflet is divided into a superior (S) and inferior (I) segment. The left ventricular outflow tract is narrow and elongated due to the anterior displacement of the AML. Note that in this plane of section the posterior mitral leaflet is not reached. R = right coronary aortic cusp, L = left coronary aortic cusp.

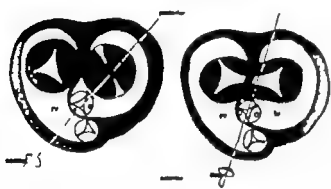


Fig 8 Diagrammatic sketch showing the position of the atrioventricular valves in normal subjects and in AVC (horizontal view). In AVC the cleft anterior mitral leaflet is positioned perpendicular to the interventricular septum rather than parallel to it as is normally the case. In order to visualise this cleft AML a rather vertical plane of section was used. In this plane of section the

posterior mitral leaflet (PML) is not visualised

characteristic however was the appearance of a break of AML echoes in diastole presumably representing the cleft of the AML (fig 3). It was formed by the lower part of the superior segment of the AML moving upwards and anterior into the LVOT while the inferior segment moved into an opposite direction downwards and posterior towards the left ventricular posterior wall. The abnormal motion pattern and the diastolic cleft of the AML were best seen with the transducer in a rather vertical position due to the displacement of the AML in these patients. The posterior mitral leaflet (PML) was usually not visualized in this plane of section. Diastolic septal apposition of the AML was observed in all cases.

In complete AVC the AML can be visualized crossing the IVS during diastole and appearing in the right ventricular cavity (S).

TRANSVERSE CROSS SECTION

The major findings in the transverse cross section at the level of the aortic root are the detection of the systolic alignment of the tricuspid and AML echoes in AVC malformation and the presence of an echo-free space in patients with complete AVC (group III) (fig 4).

# PRELIMINARY EXPERIENCES IN 1 - AND 2 - DIMENSIONAL CONTRAST ECHOCARDIOGRAPHY

K D MÜLLER F GLET J STEINBAUER AND E BÜHLMAYER

*From German Cardiac Center, Munich: Department of Pediatric Cardiology*

Brzak (5 6) and Feigenbaum (4) introduced the contrast echocardiography which primarily was used for identification of intra and extracardiac structures. Two years ago we applied this technique for identification of the excessive superior-inferior movement and wall contraction of the RVOT in children with large LRS at atrial level by 2-dimensional contrast echocardiography. At this time we injected isotonic saline solutions in a central venous catheter during routine cardiac catheterization.

During the last few years contrast echocardiography has been extended to the evaluation of blood flow patterns in patients with RLS and LRS at different levels and valvular incompetence utilizing central and recently peripheral venous injections (1 3 7 12 17).

Using this technique echo-producing agents were injected into the bloodstream and resultant echo clouds were recorded by standard echocardiographic techniques simultaneously. Explanations for the contrast phenomenon are temperature differences, turbulence, acoustic impedance differences and miniature bubbles due to a drop in pressure (2 4 8).

We investigated 12 children aged 11 days to 12 1/2 years, mean age 3 years during routine cardiac catheterization or in the early postoperative period (table 1).

(Echo-cardio-Visor Organon Teknika)

## ASPECTIVATIONS:

RV	right ventricular outflow tract
LV	left ventricular outflow tract
LA	left atrium
RA	right ventricle
RL	left ventricle
RV-L	right to left shunting
LV-R	left to right shunting
A	right to left shunting at atrial level
V	right to left shunting at ventricular level
	no right to left shunting



this level In patients with AVC-malformation normal mitral-tricuspid discontinuity at this level is replaced by mitral-tricuspid alignment due to absence of the atrioventricular septum in these patients (7)

In this study two dimensional echocardiography proved much easier to perform and much less time-consuming than M-mode scanning especially in young children and patients with Down's syndrome

### CONCLUSION

Two-dimensional multiple crystal echocardiography shows a characteristic motion pattern of the AML in patients with AVC malformation Review of the anatomy suggests that this feature represents the cleft anterior mitral leaflet Due to the abnormal position of the AML perpendicular to the interventricular septum its abnormal motion pattern is best visualized when the echo beam is adjusted accordingly

Continuously focussed multiscan provides better information than the technique used so far because of the improved lateral resolution over the entire field of view This has enabled us to visualize the cleft AML distinctly in all our patients and to diagnose AVC-malformation echocardiographically Visualization of a ventricular septal defect and size and shape of the left ventricular outflow tract give us some impression of the severity of the anomaly

### REFERENCES

- 1 BEPPU S NIMURA Y NAGATA S TAMAI H MATSUO H MATSUMOTO H KAWASASHIMA Y SAKAKIBARA H and ABE H Diagnosis of endocardial cushion defect with cross sectional and M-mode scanning echocardiography Differentiation from secundum atrial septal defect Brit Heart J 38 911 1976
- 2 BOM N LANCEE C T VAN ZWIETEN M KLOSTER E F and ROELANDT J Multiscan echocardiography I Technical description Circulation 48 1066 1976
- 3 LIGTVOET C M RIDDER J LANCEE C T HAGEMEIJER F and VLETTER W B A dynamically focussed multiscan system To be published
- 4 LIGTVOET C M VOGEL J VAN EGMOND F and VLETTER W Direct conversion of real-time two dimensional echocardiographic images Ultrasonics 89 March 1977
- 5 SAHN D J TERRY R W D ROURKE R LEOPOLD G and FRIEDMAN W F Multiple crystal echocardiographic evaluation of endocardial cushion defect Circulation 50 25 1974
- 6 SOMMERVILLE J and JEFFERSON J Left ventricular angiocardiography in atrioventricular defects Brit Heart J 30 446 1968
- 7 YOSHIKAWA J OHAKI T KATO H YOMITA Y BABA K and TANAKA K Echocardiographic diagnosis of endocardial cushion defects Jap Heart J 16 1 1975

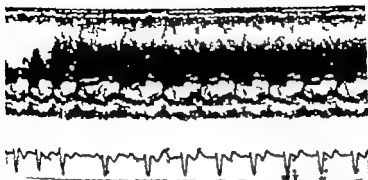


Fig 2.



Fig 3

As echoproducting agents we tested dextrose in different concentrations, physiologic saline solution, patients own blood and different human albumin solutions. We injected 3 ml in newborns and babies and 5 ml in older children, which was forthfully done by hand. So far we have no experiences with indocyanine green dye.

During the investigation the patients were supine and tracings were recorded from position I and III similar to Feigenbaum's (fig 1). Position I means dissection of the aortic root LA and RVOT, position III mitral valve level, its orifice and LVOT.

We found a similar quality of contrast patterns after peripheral as well as central injections.

Isotonic saline- or dextrose solutions gave a better contrast than injections with the patients own blood or human albumine.

In 5 cases we did not find any RLS. In 4 RLS at atrial level, one apparently through a defect interatrial patch and in other 3 children at ventricular level. So far in 4 cases the RLS demonstrated by echo techniques were documented angiocardiographically. In one case atrial and ventricular RLS could be demonstrated. In a patient with Ebstein's anomaly after Hardy's plastic and closure of the atrial septal defect at the second postopera-

1	GI	8 10 75	Laevocardia situs inv. abd. single ventricle PA	+ A
2	HH	3 2 75	Fallot pOp	-
3	RH	22 12 75	D-TGA Mustard-BromOp	+ A
4	MR	3 4 73	ASD ( Sinus venosus ) pOp	-
5	GW	10 10 72	Fallot pOp	+ V
6	DW	11 2 77	ASD I TI MI, CoA	-
7	SN	8 11 72	TA BT LK	+ A
8	RR	22 4 77	TGA + VSD	+ V
9	FM	21 3 77	Ebstein anomaly	+ A
10	WM	9 8 72	Fallot	+ V
11	WT	26 8 64	Ebstein anomaly Hardy Plastic	-
12	EW	15 4 77	pred. CoA VSD (+PA Banding)	-

We injected different solutions peripherally into the antecubital hand foot or neck veins but also centrally into the right atrium vena cava superior and inferior. In 3 cases investigated in the cath Laboratory we injected through angio-cardiographic catheters and recorded the 1-dimensional\*\* and observed or filmed the 2 dimensional cross sectional picture. In 9 children investigated in the intensive care unit we used teflon catheters or needles.

\*\* (Echo K Siemens)

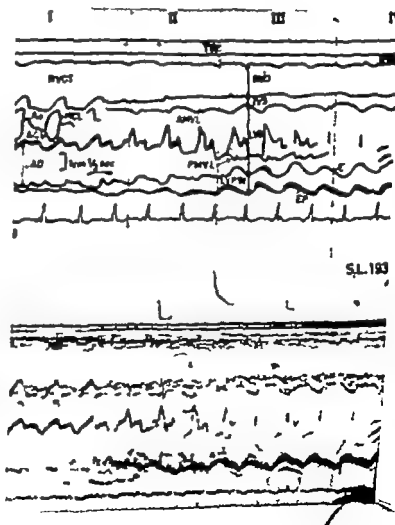


Fig 1



Fig 1



Fig 2

As echoproducing agents we tested dextrose in different concentrations physiologic saline solution patients own blood and different human albumin solutions. We injected 3 ml in newborns and babies and 5 ml in older children which was forthfully done by hand. So far we have no experiences with indocyanine green dye.

During the investigation the patients were supine and tracings were recorded from position I and III similar to Feigenbaum's (fig 1). Position I means dissection of the aortic root LA and RVOT position III mitral valve level its orifice and LVOT.

We found a similar quality of contrast patterns after peripheral as well as central injections.

Isotonic saline- or dextrose solutions gave a better contrast than injections with the patients own blood or human albumine.

In 5 cases we did not find any RLS in 4 RLS at atrial level one apparently through a defect interatrial patch and in other 3 children at ventricular level. So far in 4 cases the RLS demonstrated by echo techniques were documented angiocardialographically. In one case atrial and ventricular RLS could be demonstrated. In a patient with Ebstein's anomaly after Hardy's plastic and closure of the atrial septal defect at the second postopera-

TABLE I

1	GI	8 10 75	Laevocardia situs inv. abd. single ventricle PA	+ A
2	HH	3 2 75	Fallot pOp	-
3	RH	22 12 75	D-TGA, Mustard-Brom Op	+ A
4	MR	3 4 73	ASD ( Sinus venosus ) pOp	-
5	GW	10 10 72	Fallot p Op	+ V
6	DW	11 2 77	ASD I TI MI CoA	-
7	SN	8 11 72	TA BT LK.	+ A
8	RR	22 4 77	TGA + VSD	+ V
9	FM	21 3 77	Ebstein anomaly	+ A
10	WM	3 8 72	Fallot	+ V
11	WT	26 8 64	Ebstein anomaly Hardy Plastic	-
12	EW	15 4 77	pred. CoA VSD (+PA Banding)	-

We injected different solutions peripherally into the antecubital hand foot or neck veins but also centrally into the right atrium vena cava superior and inferior. In 3 cases investigated in the cath Laboratory we injected through angio-cardiographic catheters and recorded the 1 dimensional\*\* and observed or filmed the 2 dimensional cross sectional picture. In 9 children investigated in the intensive care unit we used teflon catheters or needles.

\*\* (Echo K Siemens)

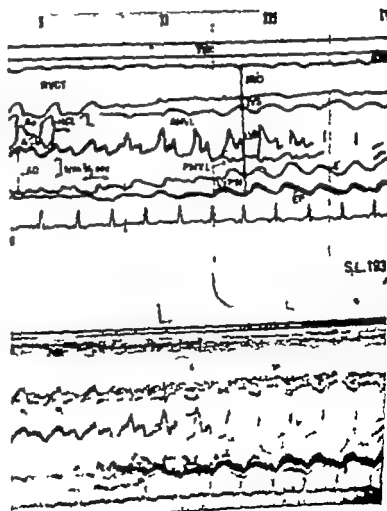


Fig 1

children demonstrated RLS at ventricular level. In a child after repair of Fallot's tetralogy in position III the contrast clouds opacified the LV via LVOT rather than through the mitral valve orifice which remains echo-free in each diastole; because non-opacified blood passes the valve. The ultrasonic reflections reached the LVOT while the mitral valve was closed. In this flow pattern echoes first appeared in the RV cavity during ventricular diastole. During the following systole echoes were seen in the LVOT early in diastole of the following cardiac cycle during the isovolumic relaxation phase.

In position I the clouds were limited to the aortic root while the LA was not filled. The opacification appears first in the RVOT during late ventricular diastole and then in the aortic root during subsequent systole.

In a 12 days old child with TGA and interatrial and interventricular RLS we found the combination of both flow patterns simultaneously (fig 4 and 5).

The timing of echo contrast flow patterns at atrial or ventricular level are in agreement with the excellent angiocardiographic analysis by Levin in 1966 and 1968 (9, 11). According to his investigations blood crosses the intraatrial septum in RLS during rapid filling phase of ventricular diastole as well as the onset of LV contraction.

Concerning interventricular shunts blood crosses from right to left at the onset of isovolumic relaxation when the LV pressure falls more rapidly than RV pressure. In patients with equal systolic ventricular pressures Levin found RLS during late ventricular ejection as well as during isovolumic relaxation.

In shunts at atrial and ventricular level Valdes-Cruz (16, 17) and Seward (18) described patterns of equal mitral as well as LV density in patients with larger atrial than ventricular shunts whereas that of scattered mitral opacification is obtained in patients with major ventricular shunting.

In summary peripheral contrast echocardiography can be used as a sensitive test for more accurate diagnosis of RLS in different cardiac lesions in ambulatory patients. Postoperative RLS can easily be evaluated by central

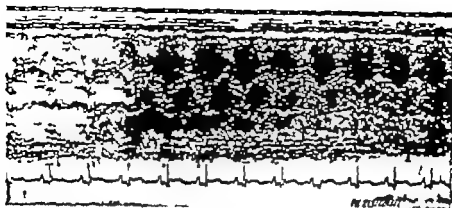


Fig 4

tive day dense clouds of echoes persisted longer due to low output state (fig 2 and 3) The contrast material - in this case 6 ml dextrose persisted for 46 cardiac cycles in the right sided heart (fig 2) In this case no intracardiac shunting could be found so the contrast echoes will be confined to the right ventricular cavity its outflow tract and the pulmonary orifice while the left sided structures remained echofree (fig 2 and 3)

In the 3 cases with RLS at atrial level we saw contrast echoes in the LA first normally during ventricular systole then in the RVOT during late diastole followed by the aortic root during subsequent systole (fig 4) In position III the most important diagnostic feature was the opacification of mitral valve orifice during diastole followed by the LVOT The echoes filled the RV cavity during ventricular diastole nearly simultaneously to the LV through the mitral valve funnel The LV filling can be delayed by one cardiac cycle

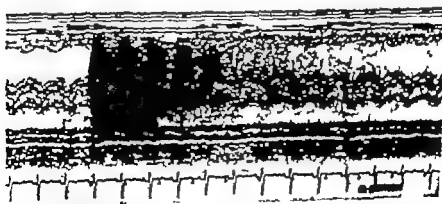


Fig 5

- 15 SHUB C TAJIK A J and SEWARD J B Detecting intrapulmonary right to-left shunts with contrast echocardiography observations in a patient with diffuse pulmonary arteriovenous fistulas Mayo Clin Proc 51 81 1976
- 16 VALDES-CRUZ L M PIERONI D R ROLAND J M ,A and SHENATEK J P Recognition of residual postoperative shunts by contrast echocardiographic techniques (abstr ) Am J Cardiol 37 178 1976
- 17 VALDES-CRUZ L.M PIERONI D R ROLAND J -M ,A and VARGHESE J Echocardiographic detection of right to left shunts by peripheral vein injections (abstr ) Circulation 52 suppl II 121 1975



contrast echocardiography Both techniques can detect and localize RLS at atrial and/or ventricular level The combination of routinely performed 1- and 2-dimensional echocardiography with ultrasound contrast techniques is safe reliable and an aid in the diagnostic assessment of children with cyanotic cardiac lesions

## REFERENCES

- 1 ASSAD-MORELL J I SEWARD J B TAJIK A J HAGLER D J GIULIANI E R and RITTER D G Echocardiographic and contrast studies in conditions associated with systemic arterial trunk overriding the ventricular septum truncus arteriosus tetralogy of Fallot and pulmonary atresia with ventricular septal defect *Circulation* 53 663 1976
- 2 BOVE A A ADAMS D F HUGH A E and LYNCH R P Cavitation at catheter tips A possible cause of air embolus *Invest Radiol* 3 159 1968
- 3 DUFF D F and GUTGESELL H P The use of saline for ultrasonic detection of a right to-left shunt in postoperative period (abstr ) *Am J Cardiol* 37 132 1976
- 4 FEIGENBAUM H STONE J M LEE D A INASSER W K and CHANG S Identification of ultrasound echoes from the left ventricle by use of intracardiac injections of indocyanine green *Circulation* 41 615 1970
- 5 GRAMIAK R and SHAH P M Echocardiography of the aortic root *Invest Radiol* 3 356 1968
- 6 GRAMIAK R SHAH P M KRAMER D H Ultrasound cardiography contrast studies in anatomy and function *Radiology* 92 939 1969
- 7 KERBER R E KIOSCHOS J M and LAUER R M Use of an ultrasonic contrast method in the diagnosis of valvular regurgitation and intracardiac shunts *Am J Cardiol* 34 722 1974
- 8 KREMKAU F W GRAMIAK R and CARSTENSEN E L Ultrasonic detection of cavitation of catheter tips *Am J Roentgenol Radium Ther Nucl Med* 110 177 1970
- 9 LEVIN A R SPACH M S BOINEAU J P CANENT R V CAPP M P and JEWETT P H Atrial pressure flow dynamics in atrial septal defects (secundum type) *Circulation* 37 476 1968
- 10 LEVIN A R SPACH M S CANENT R V and BOINEAU J P Intracardiac pressure flow dynamics in isolated ventricular septal defects *Circulation* 35 430 1967
- 11 LEVIN A R BOINEAU J P SPACH M S CANENT R V CAPP M P and ANDERSON P A W Ventricular pressure-flow dynamics in tetralogy of Fallot *Circulation* 34 4 1966
- 12 PIERONI D VARGHESE P J and ROME R D Echocardiography to detect shunt and valvular incompetence in infants and children (abstr ) *Circulation* 48 suppl IV-81 1973
- 13 SAHN D J ALLEN H D HARRIS T R GEORGE W L and GOLDBERG S J Noninvasive assessment of cardiocirculatory patterns in critically ill neonates using a saline contrast ultrasound technique 3 World Congress of Ultrasound in Medicine San Francisco Aug 1 2 1975 113
- 14 SEWARD J B TAJIK A J SPANGLER J G and RITTER D G Echocardiographic contrast studies initial experience *Mayo Clin Proc* 50 163 1975

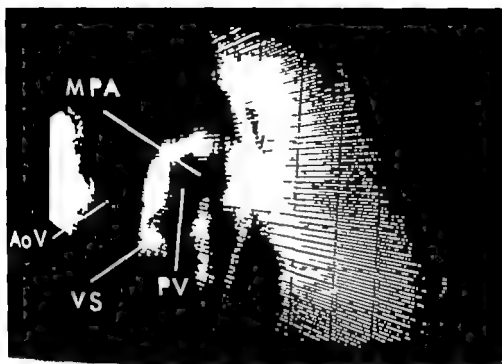


Fig 1 Longitudinal scan infant with TGA

VS ventricular septum. AoV = aortic valve PV - pulmonary valve  
MPA main pulmonary artery

# ECHOCARDIOGRAPHIC IDENTIFICATION OF THE AORTA AND PULMONARY ARTERY IN TRANSPOSITION OF THE GREAT ARTERIES

A B HOUSTON N L GREGORY E N COLEMAN AND A SHAW,

*From Royal Hospital for Sick Children and Department of Clinical Physics and Bio-engineering Glasgow*

The echocardiographic diagnosis of transposition of the great arteries (TGA) has come to depend on the demonstration of an abnormal relationship between the great arteries no reliable echocardiographic technique has emerged for the separate identification of the aorta and main pulmonary artery (MPA). A mechanical  $60^{\circ}$  sector scanner providing a two dimensional echocardiogram has now been used to identify both great arteries in 14 children up to the age of 20 months (including five within the neonatal period) with complete TGA and two infants with primitive ventricle and TGA. In a longitudinal scan the pulmonary artery is characterised by its posteriorly directed course immediately beyond the pulmonary valve and the aorta by its retrosternal course upwards before arching posteriorly. Two-dimensional transverse scans demonstrate the exact spatial relationship of the great arteries. With this wide angle scanner a firm diagnosis of TGA may be achieved in as little as one minute. The MPA can also be identified by M-mode echocardiography alone upwards angulation of the transducer from the pulmonary valve demonstrates apparent widening of the vessel corresponding to the posteriorly directed course of the MPA. The accurate assessment of great artery relationships and the positive identification of both great arteries will facilitate the echocardiographic diagnosis of other and more complex anomalies of the ventricular outlets.

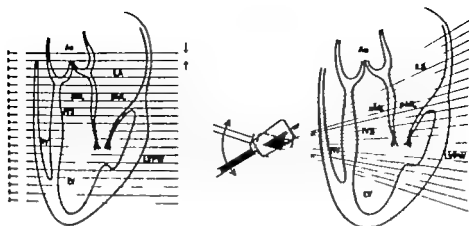


Fig 1 Schematic drawings of a longitudinal cross-section of the heart along the long-axis of the left ventricle together with indication of ultrasonic beams from the twenty elements of a multi-element transducer (left) and ultrasonic beams from an ordinary transducer used during M-mode scanning (right). The two vertical arrows in the left part of the figure point to the distance between two adjacent transducers in the multi-element transducer.

## MULTI-ELEMENT AUTOMATIC SEQUENTIAL LINE-SELECTION

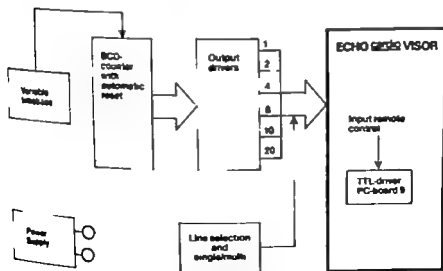


Fig 2 Block-diagram of the device used for automatic sequential line selection. BCD-counter - Binary Coded Decimal counter

In order to make such an investigation easier a simple device was constructed that enables this sequential line selection to be made automatically at

# SINGLE-ELEMENT ECHOCARDIO-TOMOGRAPHY BY MULTI-ELEMENT AUTOMATIC SEQUENTIAL LINE-SELECTION

N -R LUNDSTRÖM AND R HANSSON

*From the Department of Pediatric Cardiology University Hospital Lund  
Sweden*

In echocardiography using the single-element technique M-mode scanning plays an important role. M-mode scanning means as is well known that a continuous recording is made while the direction of the transducer is changed. By this method it is possible using a single ultrasonic beam to demonstrate relations and connections between different intracardiac structures. It is therefore not surprising that this method has been used very often in pediatric cardiology and in evaluation of complex congenital malformations of the heart. This method can provide some sort of two-dimensional impression of cardiac structures. There is however some drawbacks of the method. The final resulting M-mode scan is to a large extent depending upon the speed of the scanning manoeuvre and this can hardly be standardized. The M-mode scan therefore does not allow measurements of distances along the scanning axis. The scanning will cover a triangular area (Fig 1). This will however be displayed in rectangular form resulting in distortion of the geometric shape especially of the anterior structures.

The M-mode scanning thus seems unsuitable for demonstration of geometric shape. Such information is of course available by two dimensional echocardiography (Fig 1). So far the resolution of the two-dimensional echocardiographic recordings has however not been comparable to that of M-mode echocardiography.

In two-dimensional echocardiography using the multi element system (Bom et al 1973) a single-element M-mode echocardiogram can be obtained along any of the twenty lines used in this system. By making short single-element M-mode echocardiograms along all these lines starting with line no 1 and ending with line 20 a sort of two-dimensional picture can be obtained and particularly a picture that shows the various intracardiac structures with a more true demonstration of geometric form and shape. By doing this manually it is however difficult to avoid changing the position of the transducer during the examination and thereby making this examination of less interest.

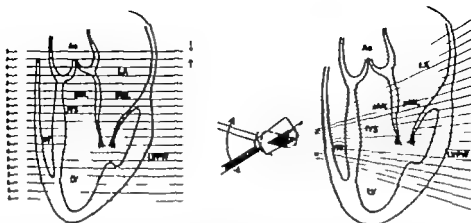


Fig 1 Schematic drawings of a longitudinal cross-section of the heart along the long-axis of the left ventricle together with indication of ultrasonic beams from the twenty elements of a multi-element transducer (left) and ultrasonic beams from an ordinary transducer used during M-mode scanning (right). The two vertical arrows in the left part of the figure points to the distances between two adjacent transducers in the multi-element transducer.

## MULTI-ELEMENT AUTOMATIC SEQUENTIAL LINE SELECTION

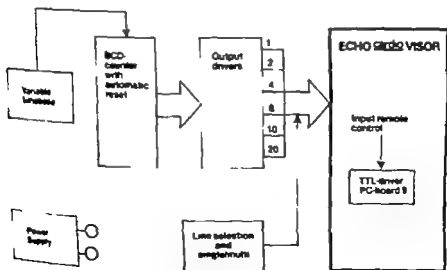


Fig 2. Block-diagram of the device used for automatic sequential line selection. BCD-counter Binary Coded Decimal counter

In order to make such an investigation easier a simple device was constructed that enables this sequential line selection to be made automatically at

# SINGLE-ELEMENT ECHOCARDIO-TOMOGRAPHY BY MULTI-ELEMENT AUTOMATIC SEQUENTIAL LINE-SELECTION

N -R LUNDSTRÖM AND R HANSSON

*From the Department of Pediatric Cardiology University Hospital Lund  
Sweden*

In echocardiography using the single-element technique M-mode scanning plays an important role. M-mode scanning means as is well known that a continuous recording is made while the direction of the transducer is changed. By this method it is possible using a single ultrasonic beam to demonstrate relations and connections between different intracardiac structures. It is therefore not surprising that this method has been used very often in pediatric cardiology and in evaluation of complex congenital malformations of the heart. This method can provide some sort of two-dimensional impression of cardiac structures. There is however some drawbacks of the method. The final resulting M-mode scan is to a large extent depending upon the speed of the scanning manoeuvre and this can hardly be standardized. The M-mode scan therefore does not allow measurements of distances along the scanning axis. The scanning will cover a triangular area (Fig 1). This will however be displayed in rectangular form resulting in distortion of the geometric shape especially of the anterior structures.

The M-mode scanning thus seems unsuitable for demonstration of geometric shape. Such information is of course available by two-dimensional echocardiography (Fig 1). So far the resolution of the two-dimensional echocardiographic recordings has however not been comparable to that of M-mode echocardiography.

In two-dimensional echocardiography using the multi-element system (Bom et al 1973) a single-element M-mode echocardiogram can be obtained along any of the twenty lines used in this system. By making short single-element M-mode echocardiograms along all these lines starting with line no 1 and ending with line 20 a sort of two-dimensional picture can be obtained and particularly a picture that shows the various intracardiac structures with a more true demonstration of geometric form and shape. By doing this manually it is however difficult to avoid changing the position of the transducer during the examination and thereby making this examination of less interest.

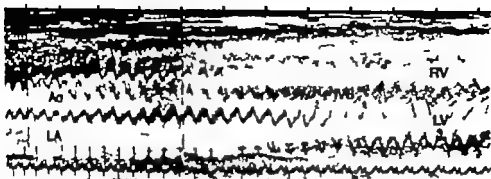


Fig 3 Echocardiogram obtained by single-element echocardiography with the transducer placed along the long-axis of the heart in a patient with Fallot's anomaly. The wide aortic root (Ao) can be seen to override the interventricular septum (IVS) separating the right ventricle (RV) from the left ventricle (LV). The echocardiogram obtained with the same transducer as Fig 3.

at the desired speed (Fig 2). The main part of this device is an automatic Binary Coded Decimal counter with automatic reset and galvanically isolated output drivers. This automatic BCD-counter has a time base that can be varied as desired. This small device has been built in a separate unit with separate power supply and connected to the multi-element echocardiographic equipment without any modification on this unit.

The multi-element 2.25 and 4.5 MHz transducers have a length of 80 mm and 7 MHz transducer a length of 50 mm which means that the distance between two adjacent single-element lines is 4 and 2.5 mm respectively (Fig 1).

Fig 3 shows a recording made with this equipment with the transducer placed along the long-axis of the left ventricle. With the transducer placed along the outflow tract of the right ventricle it can clearly be seen that the outflow tract of the right ventricle and the pulmonary artery is deviating in a posterior direction (Fig 4).

Fig 5 is another recording made with this equipment on a patient with Fallot's anomaly. The overriding of the wide aorta can clearly be demonstrated (Fig 5).

We have used this system in routine work in more than 50 patients. Echocardiograms of a quality like those shown in Figs 3-5 have been obtained in more than 90% of the patients. The main problem encountered has been to find a proper gain and reject setting suitable for all the recording levels.





Fig 3 Echocardiogram obtained by single-element echocardiography with the transducer placed along the long-axis of the left ventricle showing the normal relation between the aortic root (Ao) and the left ventricle (LV). The small markings on top of the recording show the border between the single-element echocardiogram obtained with each individual transducer of the multi-element transducer. With the 5 MHz transducer used in this recording the distance between the levels from which two adjacent N-mode recordings are obtained is 4 mm.

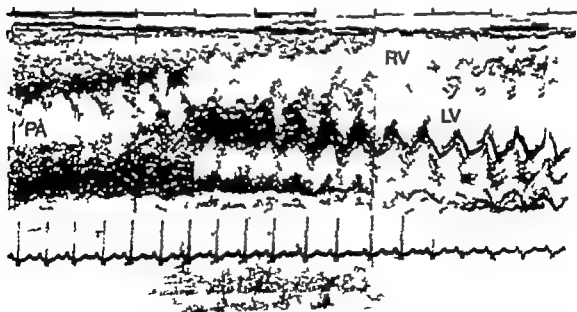


Fig 4 Echocardiogram obtained by single-element echocardiography with the transducer placed along the outflow tract of the right ventricle. The posterior deviation of the outflow tract of the right ventricle (RV) and the pulmonary artery (PA) is demonstrated. The echocardiogram obtained with the same transducer as Fig 3.

# ECHOCARDIOGRAPHIC FINDINGS IN CARDIAC TAMPONADE

K. J. HAGEL

*From the Department of Pediatric Cardiology (Prof. Dr. Rusterberg)  
Center of Pediatrics University of Gießen, German Federal Republic*

The echocardiographic findings of two pediatric patients (6 and 13-year-old) with clinical evidence of cardiac tamponade are demonstrated. The recordings were made immediately before and after pericardial drainage. The most diagnostic finding for cardiac tamponade in both cases was a reduction of the atrial E-F slope due to a decreased diastolic compliance of the heart with impaired left ventricular filling. The abnormal motion of the pulmonary valve, diminished aortic wall movement and periodic changes of the ventricular diameters are demonstrated and discussed.

In 1955 Edler (2) was the first to use ultrasound in the diagnosis of pericardial effusion. Feigenbaum (3) drew attention to this method in 1965 showing the clinical usefulness and accuracy of the new diagnostic procedure. Most following reports deal with technical comments of detecting the pericardial effusion and with its quantitative assessment (4, 6). Till now only few investigators looked for a possibility to ascertain the dramatic complication of pericardial effusion: cardiac tamponade with ultrasound (1, 5).

Therefore we want to demonstrate in the following the echocardiographic findings in two pediatric cases of cardiac tamponade. The investigations were performed on an Echocardiograph connected to a stripchart Honeywell recorder. 4.5 and 5.0 MHz unfocused transducers with an outer diameter of 0.5 cm and 1.0 cm were used.

In both children the investigation was quite difficult because they showed marked dyspnea and were very anxious so they could not lie quiet for a longer period in standard supine position. The echocardiograms were recorded just before pericardial puncture or pericardiectomy and immediately afterwards.

Case 1 Ch. H. a 13-year-old girl. Three weeks before admission she felt ill with fatigue, fever and seldom vomiting. On admission the girl showed respi-

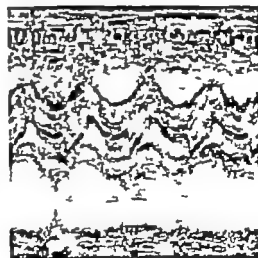
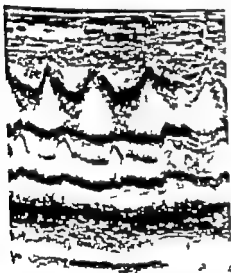
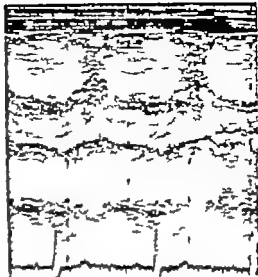
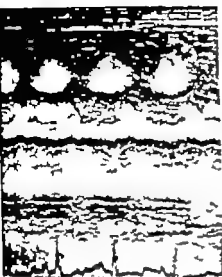
A change of the reject control is however possible during the recording

A further improvement in resolution could be obtained by a pre set pattern of time-gain compensation for each line used. Such an arrangement would also improve the resolution in the two-dimensional picture

Since these recordings are made by single element M-mode technique in sequential levels along a multi element transducer we have called it single-element echocardio tomography or ECT

#### REFERENCE

1. BOM N, LANCEE C T, VAN ZWIETEN G, KLOSTER F E, and ROELANDT J  
Multiscan echocardiography I. Technical description; Circulation 48 1066  
1973



A

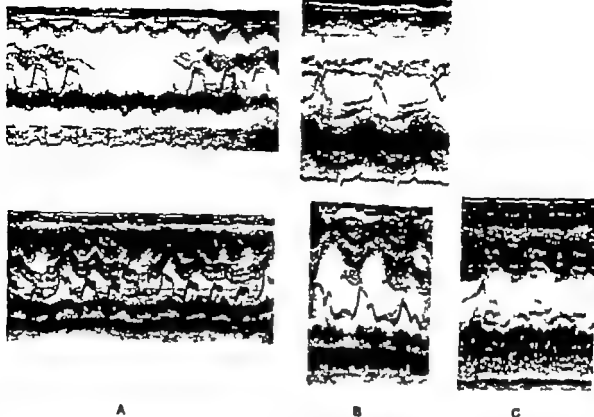
B

Fig 3 -- Aortic wall movement with improvement after pericardiocentesis (B)

In cardiac tamponade the diastolic echos of the pulmonary valve was almost horizontal and no a-wave could be detected (Fig 3 A) After decompression of the heart there was a constant a-wave of about 5 mm (Fig 3 B)

The only echocardiographic finding that did not change after drainage of the pericardium was the normal movement of the tricuspid valve (Fig 4)

Case 2 A. Sch a 6 year-old boy Two weeks before admission in our hospital he had first signs of chickenpox with a normal course in the beginning



*Fig 1 A Both cases in cardiac tamponade with a large pericardial effusion anterior and posterior of the heart. The EF-slope of the mitral valve is reduced. B After decompression of the heart the EF-slope is normal in both cases although in case 2 there is still a large effusion.*

ratory distress, hepatomegaly and elevated jugular venous pressure. The ECG was normal except a relative low voltage. There was no electrical and mechanical alternans. The chest roentgenogram showed an enlargement on both sides of the cardiac silhouette. The now performed echocardiogram revealed a large pericardial effusion anterior and posterior of the heart (Fig 1 A).

The anterior mitral valve showed a clear reduction in the early diastolic closing movement. The posterior mitral valve moved opposite like normal. In systole a prolapse pattern of both mitral valves was recorded (Fig 1 A).

The puncture of the pericardium was performed and we removed about 800 ml of a sero sanguineous fluid. The echocardiogram of the mitral valve movement was now normal with normal E F slope (Fig 1 B). Both right and left ventricular enddiastolic diameters were still enlarged.

In Fig 2 before drainage of the pericardium the aortic wall movement was reduced and showed a slight improvement afterwards.



Case 1

*Fig 1 Tricuspid valve movement with normal E-slope before and after drainage of the pericardial effusion.*



Case 2

Mitral valve was decreased. The posterior mitral valve moved backwards. In contrast to case 1 we saw here periodic changes in the diameter of the right and left ventricle (Fig 1 A)

After puncture of the pericardium with removal of 350 ml fibrinous fluid the boy was soon in a much better general condition with only mild respiratory distress.

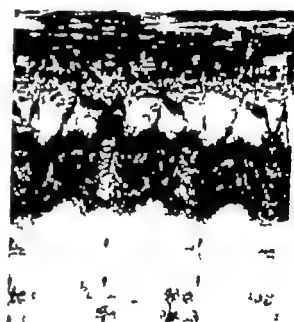
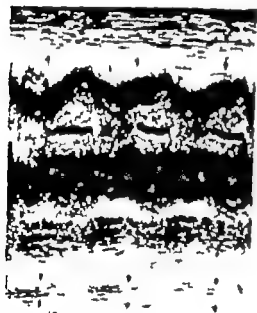
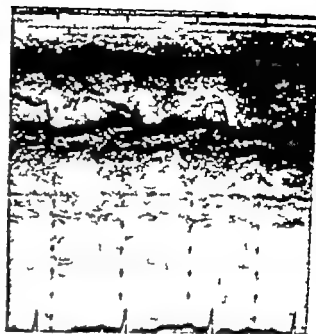
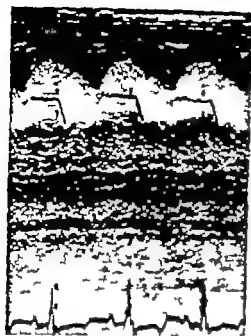
In the afterwards performed echocardiographic recording the E-F slope of the mitral valve was normal although a large amount of pericardial fluid anterior and posterior of the heart was still present (Fig 1 B)

When pericardiectomy had been performed with removal of about 500 ml of a serosanguinous fluid the echocardiogram immediately afterwards showed an identical normal E F slope (Fig 1 C)

In addition to these mitral findings there were almost the same changes in the aortic wall movement and the echoes of the pulmonic valve before and after the pericardial drainage as described in case 1

Identical to case 1 the pulmonary valve is recorded with an almost horizontal E F slope and a nearly absent a-wave (Fig 3 A) After decompression of the heart the a wave is 7 mm deep (Fig 3 B)

The unchanged normal motion pattern of the tricuspid valve is also recorded (Fig 4)



A

B

*Fig 3 A Pulmonic valve recording in cardiac tamponade with almost absent a-wave B After decompression of the heart the a-wave is 5 mm in case 1 and 7 mm in case 2*

10 days later the boy was in bad general condition with fever and cardiac malfunction. The chest roentgenogram in a outside clinic showed an extremely enlarged cardiac silhouette. On admission he was orthopneic with ascites, hepatomegaly and raised jugular venous pressure. The ECG was without abnormalities except low voltage.

The echocardiographic examination revealed a large pericardial effusion anterior and posterior to the heart. Similar to case 1 the EF slope of the

## REFERENCES

1. CRUZ JA, COHEN HC, PRABHU R, GLICK G. Diagnosis of cardiac tamponade by echocardiography. *Circulation* 52: 460 1975
2. EDLER I. The diagnostic use of ultrasound in heart disease. *Acta Medica Scand Suppl* 308: 32 1955
3. FEIGENBAUM WALDHUSEN JA, HYDE LP. Ultrasound diagnosis of pericardial effusion. *JAMA* 191: 711 1965
4. FEIGENBAUM H. Echocardiographic diagnosis of pericardial effusion. *Am J Cardiol* 26: 475 1970
5. FEIGENBAUM H, ZAKY A, GRABHORN LL. Cardiac motion in patients with pericardial effusion. A study using reflected ultrasound. *Circulation* 34: 611 1966
6. GOLDBERG BB, OSTRUM BJ, ISARD JJ. Ultrasonic determination of pericardial effusion. *JAMA* 202: 927 1967
7. KANDA MC, GRAMIAK R, GROSS CM. Echocardiography of cardiac valves in pericardial effusion. *Circulation* 54: 600 1976
8. QUINONES MA, GAASCH MH, WAISSER E, ALEXANDER JK. Reduction in rate of diastolic descent of the mitral valve echogram in patients with altered left ventricular diastolic pressure-flow relations. *Circulation* 49: 246 1974



We demonstrated these two pediatric cases because we believe that these findings may be helpful in the diagnosis of cardiac tamponade. The most remarkable finding seems to be the reduction of the E-F slope of the mitral valve in both cases similar to 3 cases of cardiac tamponade of D CRUZ (1) due to a decreased diastolic compliance of the left heart with impaired left ventricular filling as QUINONES (8) reported in connection with other cardiac diseases. He found a good correlation between the mitral valve slope and the enddiastolic distensibility index. In cardiac tamponade this index is reduced and therefore also the E-F slope of the mitral valve. NANDA and GRAMIAX (7) lately demonstrated abnormal motions of cardiac valves and other structures in large pericardial effusion which all normalises after removal of the pericardial fluid. They claim that there should be no diagnostic and therapeutic conclusion out of these abnormal findings. In case 2 we could demonstrate that there was a significant acceleration of the mitral valve E-F slope after only partial removal of the pericardial fluid. We therefore think that this constant finding of the E-F slope is a diagnostic hint for cardiac tamponade.

The pulmonary valve tracings in cardiac tamponade in case 1 and 2 are diagnostic signs of pulmonary hypertension secondary to pulmonary venous obstruction.

The shown diminished aortic wall movement does not seem to be a good indicator for low cardiac output.

D CRUZ (1) tried to show in 3 cases of cardiac tamponade that with paradoxical pulse during inspiration left ventricular filling and stroke volume decreases. Only in our case 2 similar periodic changes in the left ventricular diameters were recorded but without registration of respiration. Measurement of ventricular size seems to be very difficult when the heart like in cardiac tamponade is in no constant position but is swinging in the fluid filled pericardium. We therefore do not believe that reproducible measurements of the ventricular diameters is possible.

In conclusion we hope that our findings in addition to reports of others will help to find a proven way in the echocardiographic diagnosis of cardiac tamponade.

# REFERENCES

1. BOKUZ JA COHEN HC PRABHU R GLICK G Diagnosis of cardiac tamponade by echocardiography *Circulation* 52 460 1975
2. EDLER I The diagnostic use of ultrasound in heart disease *Acta Medica Scand Suppl* 308 32 1955
3. FEIGENBAUM WALDHAUSEN JA HYDE LP Ultrasound diagnosis of pericardial effusion *JAMA* 191 711 1965
4. FEIGENBAUM H Echocardiographic diagnosis of pericardial effusion *Am J Cardiol* 26 475 1970
5. FEIGENBAUM H ZAKY A GRABHORN LL Cardiac motion in patients with pericardial effusion. A study using reflected ultrasound *Circulation* 34 611 1966
6. GOLDBERG BB OSTRIUM BJ ISARD JJ Ultrasonic determination of pericardial effusion *JAMA* 202 927 1967
7. RAPHA HC GRAMIAK R GROSS CM Echocardiography of cardiac valves in pericardial effusion *Circulation* 54 500 1976
8. QUTUBIDES MA GAASCH MH WATISSER E ALEXANDER JK Reduction in rate of diastolic descent of the mitral valve echogram in patients with altered left ventricular diastolic pressure-flow relations *Circulation* 49 246 1974

# ECHOCARDIOGRAPHIC FINDINGS IN VENTRICULAR SEPTAL RUPTURE AND ANTERIOR WALL ANEURYSM COMPLICATING MYOCARDIAL INFARCTION

H EGEBLAD AND S HAUNSD

*From the Department of Cardiology Copenhagen County Hospital  
Gentofte Denmark*

## ABSTRACT

Echocardiographic findings in a patient with ventricular septal rupture and anterolateral wall aneurysm complicating myocardial infarction are presented. The findings were confirmed by cardiac catheterization and surgery. Using M-mode ultrasonocardiography one was able to demonstrate and localize the aneurysm as well as the ventricular septal defect which presented as an oblique inter-ventricular communication appearing only during systole. Thus echocardiography supplemented the invasive examinations in exactly revealing the site of ventricular septal rupture. Other echocardiographic features of ventricular septal rupture were right ventricular dilatation, pathological septal motion and abnormal tricuspid valve motion as recently reported by other authors.

Ventricular septal rupture (VSR) is a rare complication of acute myocardial infarction (0.5-1%) (5). VSR is presented by the sudden occurrence of a systolic murmur accompanied by clinical deterioration. There is a common association with left ventricular aneurysms and the prognosis is grave (5). Since surgical correction is not infrequently feasible, accurate diagnosis is important. Cardiac catheterisation and selective coronary arteriography are generally required. As presented in this paper, echocardiography too provides valuable information.

## CASE STORY

A 48 year old woman was admitted to hospital with an anterior transmural myocardial infarction. Except for treated hypertension and a present RBBB there was no previous history of cardiovascular disease. Four hours after admission the condition abruptly aggravated. Severe hypotension occurred and simultaneously a loud systolic murmur was noticed. The patient did not succumb to the acute exacerbation but she recovered only slowly and though treated with digoxin.

and diuretics she was persistently characterized by cardiac failure on very little effort. Subsequently five months after the acute infarction the patient was transferred to the department of cardiology Copenhagen County Hospital Gentofte.

Clinical examination revealed no signs of cardiac failure at rest. The blood pressure however was 110/80 and the pulse rate 100. Abnormal systolic pulsation and a thrill was felt outside the midclavicular line. A grade 5/6 holosystolic harsh murmur with maximum at the apex and the lower left sternal border radiating to the axilla was heard. ECG revealed sinus rhythm, right bundle branch block (RBBB) and anterior infarction with persistent S-T segment elevations. Chest X ray demonstrated cardiomegaly and a large bulge at the left contour of the heart.

#### ECHOCARDIOGRAPHIC FINDINGS

Echocardiograms were performed using SKI Ekoline 20 ultrasonic apparatus connected to a Tektronix oscilloscope. The ultrasonic frequency was 2.5 MHz and the transducer focused at 10 cm. M-mode recordings were obtained on Polaroid<sup>®</sup> prints using open shutter technique. The patient was examined in the supine position.

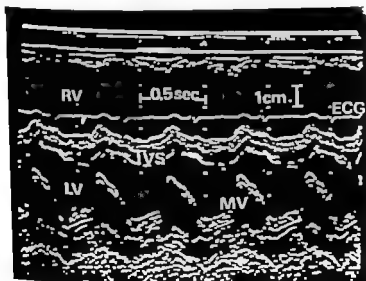


Fig. 1. Echocardiogram obtained from the left fourth intercostal space at the sternal border. The recording demonstrates right ventricular dilatation while the left ventricle is not dilated. The interventricular septum is almost stationary during systole and exhibits in diastole a diphasic motion pattern which to a certain extent resembles the echocardiogram of the anterior mitral cusp. RV: right ventricle, LV: left ventricle, IVS: interventricular septum, MV: mitral valve, ECG: electrocardiogram.

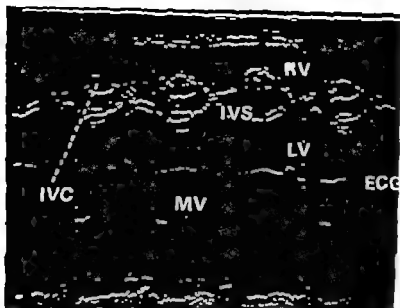


Fig 2 M-mode recording obtained from the left fifth intercostal space in the midclavicular line. During systole the interventricular septum (IVS) is splitted into two layers separated by an echofree zone which represents an obliquely passing communication (IVC) connecting the left (LV) to the right ventricle (RV). MV fragments of the anterior mitral leaflet. ECG electrocardiogram. Same units as in fig 1.

Fig 1 is obtained from the left fourth intercostal space at the sternal border. The echocardiogram primarily demonstrates right ventricular dilatation while the left ventricle in this diameter near the basis of the ventricle not exceeds normal values (6). The recording of the interventricular septum shows in diastole a diphasic pattern with a certain resemblance to an M-mode recording of the anterior mitral leaflet. During systole the septum is almost a kinetic and the systolic thickening is severely reduced. The mitral valve echocardiogram is essentially normal.

Fig 2 is performed with the transducer positioned in the midclavicular line in the fifth intercostal space. The ultrasonic beam is aiming at the interventricular septum just inferior to the area recorded in fig 1. The motion pattern of the ventricular septum is extraordinary. During systole the septum is divided into a thin right sided membrane with paradoxical movement and a somewhat thicker tissue-layer which moves towards the cavity of the left ventricle. The two laminae described are separated by an echofree zone which represents an interventricular communication. Thus the echocardiogram in fig 2 demonstrates a ventricular septal defect appearing only during systole and passing obliquely through the upper muscular part of the septum.

Recordings in the fifth and sixth left intercostal spaces at an area between the midclavicular and anterior axillary line exhibited paradoxical motion of the anterior heart wall (fig 3). The posterior wall of this expansion of the heart was characterized by immotility or slight paradoxical motion. These findings indicated a laterally located aneurysm.

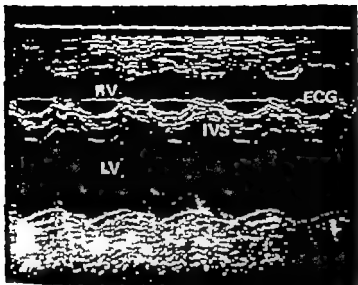


Fig 3 Echocardiogram obtained from the left sixth intercostal space two cm lateral to the midaxillary line. The recording illustrates paradoxical motion of the anterior wall of the right ventricle. Septal motion as demonstrated in fig 1. RV right ventricle, LV left ventricle, IVS interventricular septum, ECG electrocardiogram. Same unit as in fig 1.

Other echocardiograms revealed normal aortic valve echoes, left atrial size within normal limits and normal posterior wall excursions except for the minor part involved in the aneurysm. The tricuspid valve echocardiogram presented in some recordings a flattened EF slope. In other recordings however the diastolic pattern was completely normal.

#### FINDINGS AT CARDIAC CATHETERIZATION AND OPERATION

A pulmonary hypertension (58/26 mm Hg) and a left to right shunt of 3 l at the ventricular level was found. Left ventricular angiocardigrams revealed in right anterior oblique position a large anterolaterally located aneurysm but no regurgitation to the left atrium. Left anterior oblique angiocardigrams proved simultaneous contrast filling of the conus of the right ventricle. The exact position of the shunt however was impossible to define. Coronary arteriography a  $\alpha$  Judkins demonstrated subtotal occlusion of the left anterior descending branch of the left coronary artery 4 cm distal to the bifurcation. Other coronary artery branches were all normal. At surgery an aneurysm measuring 8 cm in diameter and involving the anterolateral wall of the heart was removed. Four slit like ruptures each measuring approximately 0.8 cm along the major axis and located in the upper part of a fibrously degenerated muscular septum were repaired. No reconstructive coronary artery surgery was required.

#### DISCUSSION

A recurrent diagnostic problem in acute myocardial infarction is the distinction between ventricular septal rupture and mitral regurgitation caused by

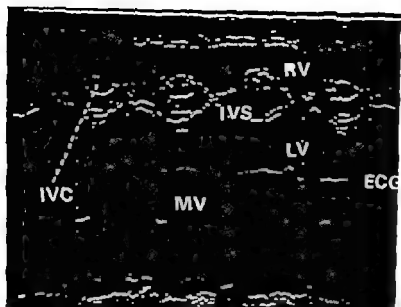


Fig 2 M-mode recording obtained from the left fifth intercostal space in the midclavicular line. During systole the interventricular septum (IVS) is splitted into two layers separated by an echofree zone which represents an obliquely passing communication (IVC) connecting the left (LV) to the right ventricle (RV). MV fragments of the anterior mitral leaflet. ECG electrocardiogram. Same units as in fig 1.

Fig 1 is obtained from the left fourth intercostal space at the sternal border. The echocardiogram primarily demonstrates right ventricular dilatation while the left ventricle in this diameter near the basis of the ventricle not exceeds normal values (6). The recording of the interventricular septum shows in diastole a diphasic pattern with a certain resemblance to an M-mode recording of the anterior mitral leaflet. During systole the septum is almost a kinetic and the systolic thickening is severely reduced. The mitral valve echocardiogram is essentially normal.

Fig 2 is performed with the transducer positioned in the midclavicular line in the fifth intercostal space. The ultrasonic beam is aiming at the interventricular septum just inferior to the area recorded in fig 1. The motion pattern of the ventricular septum is extraordinary. During systole the septum is divided into a thin right-sided membrane with paradoxical movement and a somewhat thicker tissue-layer which moves towards the cavity of the left ventricle. The two laminae described are separated by an echofree zone which represents an interventricular communication. Thus the echocardiogram in fig 2 demonstrates a ventricular septal defect appearing only during systole and passing obliquely through the upper muscular part of the septum.

Recordings in the fifth and sixth left intercostal spaces at an area between the midclavicular and anterior axillary line exhibited paradoxical motion of the anterior heart wall (fig 3). The posterior wall of this expansion of the heart was characterized by immotility or slight paradoxical motion. These findings indicated a laterally located aneurysm.

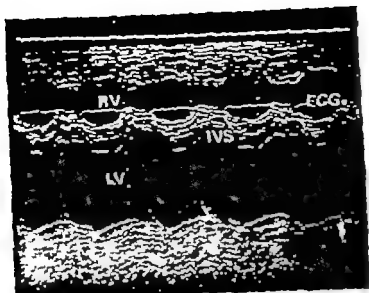


Fig 3 Echocardiogram obtained from the left sixth intercostal space two cm lateral to the midclavicular line. The recording illustrates paradoxical motion of the anterior wall of the right ventricle. Septal motion as demonstrated in fig 1. RV right ventricle, LV left ventricle, IVS interventricular septum, ECG electrocardiogram. Same unit as in fig 1.

Other echocardiograms revealed normal aortic valve echoes, left atrial size within normal limits and normal posterior wall excursions except for the minor part involved in the aneurysm. The tricuspid valve echocardiogram presented in some recordings a flattened EF slope. In other recordings however the diastolic pattern was completely normal.

#### FINDINGS AT CARDIAC CATHETERIZATION AND OPERATION

A pulmonary hypertension (58/26 mm Hg) and a left to right shunt of 3 l at the ventricular level was found. Left ventricular angiocardiograms revealed in right anterior oblique position a large anterolaterally located aneurysm but no regurgitation to the left atrium. Left anterior oblique angiocardiograms proved simultaneous contrast filling of the cones of the right ventricle. The exact position of the shunt however was impossible to define. Coronary arteriography as in Judkins demonstrated subtotal occlusion of the left anterior descending branch of the left coronary artery 4 cm distal to the bifurcation. Other coronary artery branches were all normal. At surgery an aneurysm measuring 8 cm in diameter and involving the anterolateral wall of the heart was removed. Four slit like ruptures each measuring approximately 0.8 cm along the major axis and located in the upper part of a fibrously degenerated muscular septum were repaired. No reconstructive coronary artery surgery was required.

#### DISCUSSION

A recurrent diagnostic problem in acute myocardial infarction is the distinction between ventricular septal rupture and mitral regurgitation caused by



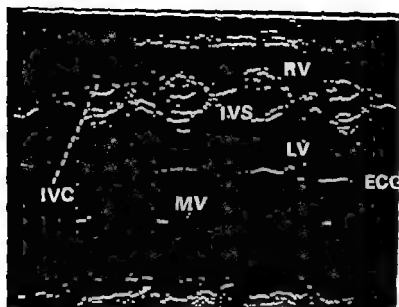


Fig 1 is obtained from the left fourth intercostal space at the sternal border. The echocardiogram primarily demonstrates right ventricular dilatation while the left ventricle in this diameter near the basis of the ventricle not exceeds normal values (6). The recording of the interventricular septum shows in diastole a diphasic pattern with a certain resemblance to an M-mode recording of the anterior mitral leaflet. During systole the septum is almost a kinetic and the systolic thickening is severely reduced. The mitral valve echocardiogram is essentially normal.

Fig 2 is performed with the transducer positioned in the midclavicular line in the fifth intercostal space. The ultrasonic beam is aiming at the interventricular septum just inferior to the area recorded in fig 1. The motion pattern of the ventricular septum is extraordinary. During systole the septum is divided into a thin right-sided membrane with paradoxical movement and a somewhat thicker tissue layer which moves towards the cavity of the left ventricle. The two laminae described are separated by an echo-free zone which represents an interventricular communication. Thus the echocardiogram in fig 2 demonstrates a ventricular septal defect appearing only during systole and passing obliquely through the upper muscular part of the septum.

Recordings in the fifth and sixth left intercostal spaces at an area between the midclavicular and anterior axillary line exhibited paradoxical motion of the anterior heart wall (fig 3). The posterior wall of this expansion of the heart was characterized by immotility or slight paradoxical motion. These findings indicated a laterally located aneurysm.

Fig 2 M-mode recording obtained from the left fifth intercostal space in the midclavicular line. During systole the interventricular septum (IVS) is splitted into two layers separated by an echo-free zone which represents an obliquely passing communication (IVC) connecting the left (LV) to the right ventricle (RV). MV fragments of the anterior mitral leaflet. ECG electrocardiogram. Same write as in fig 1.

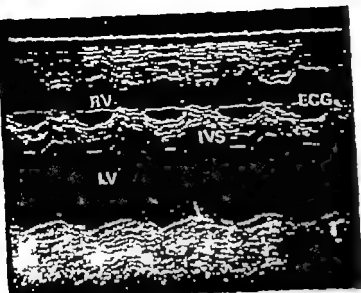


Fig 3 Echocardiogram obtained from the left sixth intercostal space two cm lateral to the midclavicular line. The recording illustrates paradoxical motion of the anterior wall of the right ventricle. Septal motion as demonstrated in fig 1. RV right ventricle, LV left ventricle, IVS interventricular septum, ECG electrocardiogram. Some writ as in fig 1

Other echocardiograms revealed normal aortic valve echoes, left atrial size within normal limits and normal posterior wall excursions except for the minor part involved in the aneurysm. The tricuspid valve echocardiogram presented in some recordings a flattened EF slope. In other recordings however the diastolic pattern was completely normal.

#### FINDINGS AT CARDIAC CATHETERIZATION AND OPERATION

A pulmonary hypertension (58/26 mm Hg) and a left to right shunt of 3:1 at the ventricular level was found. Left ventricular angiocardiograms revealed in right anterior oblique position a large anterolaterally located aneurysm but no regurgitation to the left atrium. Left anterior oblique angiocardiograms proved simultaneous contrast filling of the conus of the right ventricle. The exact position of the shunt however was impossible to define. Coronary arteriography a m Judkins demonstrated subtotal occlusion of the left anterior descending branch of the left coronary artery 4 cm distal to the bifurcation. Other coronary artery branches were all normal. At surgery an aneurysm measuring 3 cm in diameter and involving the anterolateral wall of the heart was removed. Four slit like ruptures each measuring approximately 0.5 cm along the major axis and located in the upper part of a fibrously degenerated muscular septum were repaired. No reconstructive coronary artery surgery was required.

#### DISCUSSION

A recurrent diagnostic problem in acute myocardial infarction is the distinction between ventricular septal rupture and mitral regurgitation caused by

papillary muscle injury. As stated by Dugall et al (5) the clinical differentiation is unreliable. Until recently cardiac catheterization and angiography were the only methods for obtaining the exact diagnosis. Echocardiography however represents an alternative way of establishing the nature of the cardiac catastrophic event. Furthermore informations concerning the feasibility for surgical repair are obtained using ultrasound examination. Chandraratna et al (3) established right ventricular dilatation as the most salient echocardiographic feature of VSR. Silverman et al however was unable to demonstrate right ventricular dilatation in one of three patients examined within few hours of ventricular septal rupture (9). Abnormal septal motion in VSR has been reported by De Joseph et al (4) and Silverman et al (9) who also demonstrated diminished or reversed EF slope of the tricuspid valve echocardiogram. The non specific echocardiographic features of mitral insufficiency are augmented septal motion amplitude and dilatation of the left ventricle and atrium (2,6). Rupture as well as dysfunction of the chordae and papillary muscle apparatus are claimed to produce characteristic alterations of the mitral leaflet motion patterns (2,6). These pathologic findings are however not always present (8).

In the case presented echocardiographic examination revealed right ventricular dilatation while none of the signs of mitral incompetence were recorded. Furthermore the septum demonstrated not only systolic hypokinesis and subnormal thickening but also an abnormal diastolic motion pattern which was taken to account of pronounced septal fibrosis and resulting passivity to the diastolic filling of the left ventricle (RBBB does not change the motion pattern of the interventricular septum (1)).

The interventricular communication demonstrated was easy to reproduce. The possibility of recording a ventricular septal defect even with careful examination is however unpredictable. Two-dimensional realtime scanning or pulsating Doppler-examination may prove useful. According to Feigenbaum et al (7) a normal size of the basis of the left ventricle indicates a not disadvantageous prognosis of aneurysmectomy. Normal contractility of the non infarcted myocardium also demonstrated is as well important evaluating the patient for surgery (7). Thus these findings may be essential in selecting patients for further investigative and surgical procedures.

In the present case left ventricular angiocardiography demonstrated a superiorly located ventricular septal defect but was unable to point out the exact site of the shunt. Considering the RBBB which has been diagnosed prior to the infarction it was impossible to exclude a congenital defect.

(information of earlier heart auscultation were not available) The operation however finally confirmed the echocardiographic diagnosis of rupture in the upper muscular part of a firmly scarred ventricular septum

In summary echocardiography seems very suitable in diagnosed cardiac complications of acute myocardial infarction In the case presented an anterolateral aneurysm and a ventricular septal rupture were revealed Heart catheterization with selective coronary arteriography are generally required in the final evaluation for surgery In the present case however echocardiography supplemented the invasive examinations in precisely locating a ventricular septal rupture

#### REFERENCES

- 1 BEYARS L.C and RAPAPORT E An echocardiographic study of left ventricular septal and posterior wall motion in left and right bundle branch block Clin Res 21:234 1973
- 2 BURGESS J CLARK R KAMIGAKI M and COHN K Echocardiographic findings in different types of mitral regurgitation Circulation 48:97 106 1973
- 3 CHANDRANATHA P A M BALACHANDRAN P K SHAH P M and HODGES M Echocardiographic observations on ventricular septal rupture complicating acute myocardial infarction Circulation 51:506 510 1975
- 4 DE JOSEPH R.L SEIDES S F LINDNER A and DAMATO A M Echocardiographic findings of ventricular septal rupture in acute myocardial infarction Am J Cardiol 36:346 348 1975
- 5 DUGALL J C PRYOR R and BLOUNT S G Systolic murmur following myocardial infarction Am Heart J 87:577 583 1974
- 6 FEIGENBAUM H Echocardiography Lea and Febiger Philadelphia 1972
- 7 FEIGENBAUM H CORYA B C DILLON J C WEYMAN A E RASMUSSEN H BLACK M.J and CHANG S Role of echocardiography in patients with coronary artery disease Am J Cardiol 37:775 786 1976
- 8 MART D.A. PAKRASHI B C and IONESCU M I Papillary muscle rupture following myocardial infarction Thorax 28:390 393 1973
- 9 SILVERMAN B KOZMA F SILVERMAN M and KING S Echocardiographic manifestations of postinfarction ventricular septal rupture Chest 68:778 780 1975

# QUANTITATIVE ANALYSIS OF LEFT VENTRICULAR FILLING PHASE BY ECHOCARDIOGRAPHY

P BRUN C ODDOU (\*) E BERALDO A KULAS F LAURENT  
A PHILIPPON F DE VERNEJOUL

*From the Groupe de Recherche U 138 de l'INSERM Service d'Exploration  
Fonctionnelle C E U Henri Mondor Créteil France*

## ABSTRACT

The ultrasonic method was used in an attempt to correlate the different mechanical events occurring during left ventricular rapid filling phase concerning anterior mitral leaflet posterior wall and interventricular septal motions

Signals were recorded on a line scan recorder. The M-mode records were placed on a digitizing tablet under the control of a mini-computer for continuous measurements throughout the cardiac cycle. Q waves were indicated to identify end-diastole and heart rate. The left ventricular internal diameter (minor axis) and its rate of change were calculated from anterior and posterior endocardial echos together with posterior wall and septal thickness external and mid-wall diameter. The analysis was made on data obtained from 40 normal subjects

The results suggest that our echographic measurements of the left ventricular internal diameter rate of change and the electromagnetic transmitral flow time variation present a high temporal correlation:

1: Peak rate of change of the internal diameter lengthening and peak mitral flow occur shortly after the anterior mitral leaflet E wave (echographic data:  $26 \pm 30$  ms)

2: In the case of long diastole rapid lengthening and filling phase ends before mitral F point (echographic data:  $43 \pm 37$  ms)

The abrupt slope change of the posterior wall occurring during early diastole precedes significantly the end of rapid filling ( $50 \pm 30$  ms), which is indicated by an abrupt slope change of the interventricular septum

---

\* Laboratoire de Biorhéologie et d'Hydrodynamique Université Paris VII

The improved quality of time motion echocardiograms related to linescan recorders allows identification of posterior wall endocardial and epicardial echos and left and right septal endocardial echos and satisfactory measurements of both myocardial thickness and internal diameters. Routine measurements concern end-diastole and end systole and a shortening ratio (often expressed as an ejection fraction) and a thickening ratio can be derived correctly correlated with cineangiographic estimates.

So a continuous analysis of the rate of change of wall thickness and left ventricular dimensions has been proposed (1, 2, 4). Diastolic changes of short axis diameter are assumed to be related to ventricular filling properties although the left ventricle change of shape prevents satisfactory volume and flow calculations.

The purpose of this work is to analyse simultaneously during diastole and mainly during its rapid filling phase: a) the posterior wall and interventricular septum echograms (including the study of the slope changes); b) the anterior mitral leaflet echogram; c) the internal diameter rate of change. Focus is directed toward the analysis of time relations between the different mechanical events.

#### METHODS AND MATERIAL

The device employed to record the echocardiograms was the Echocardivisor (Organon Technika) which has conventional single element and multiscan capability. M-mode signals were recorded on a Honeywell linescan recorder. To record the diastolic motion of the anterior mitral leaflet the transducer was aimed toward its free edge and then slightly angulated so that on the same recording could appear septal and posterior wall echograms satisfying the requisites for left ventricular minor axis measurements. The M-mode recordings were always preceded by a dynamic mode observation so that the results of improperly oriented left ventricle (long axis and echo beam angular relationship) could be rejected.

The M-mode recording was placed on a digitizing tablet (Wang Digitizer resolution: 0.25 mm) and the selected echos were traced. This was done under the control of a Wang 2200 Calculator (16 K-octets) with a floppy disk unit and a XY plotter (fig. 1). The sampling rate was related to the recording speed (200 pc/second for a 50 mm per second speed). The following structures were recorded: a) the left and whenever possible right side of the interventricular septum; b) the anterior mitral leaflet; c) the endocardium and epicardium of the left ventricular posterior wall. Each trace was submitted to three conse-

# QUANTITATIVE ANALYSIS OF LEFT VENTRICULAR FILLING PHASE BY ECHOCARDIOGRAPHY

P BRUN C ODDOU (\*) E BERALDO A KULAS F LAURENT  
A PHILIPPON F DE VERNEJOUL

*From the Groupe de Recherches U 138 de l'INSERM Service d'Exploration  
Fonctionnelle C H U Henri Mondor Créteil France*

## ABSTRACT

The ultrasonic method was used in an attempt to correlate the different mechanical events occurring during left ventricular rapid filling phase concerning anterior mitral leaflet posterior wall and interventricular septal motions

Signals were recorded on a line scan recorder. The M-mode records were placed on a digitizing tablet under the control of a mini-computer for continuous measurements throughout the cardiac cycle. Q waves were indicated to identify end-diastole and heart rate. The left ventricular internal diameter (minor axis) and its rate of change were calculated from anterior and posterior endocardial echos together with posterior wall and septal thickness external and mid-wall diameter. The analysis was made on data obtained from 40 normal subjects

The results suggest that our echographic measurements of the left ventricular internal diameter rate of change and the electromagnetic transmitral flow time variation present a high temporal correlation:

1: Peak rate of change of the internal diameter lengthening and peak mitral flow occur shortly after the anterior mitral leaflet E wave (echographic data:  $26 \pm 30$  ms)

2: In the case of long diastole, rapid lengthening and filling phase ends before mitral F point (echographic data  $43 \pm 37$  ms)

The abrupt slope change of the posterior wall occurring during early diastole precedes significantly the end of rapid filling ( $50 \pm 30$  ms) which is indicated by an abrupt slope change of the interventricular septum

\* Laboratoire de Biorhéologie et d'Hydrodynamique Université Paris VII

The improved quality of time motion echocardiograms related to linescan recorders allows identification of posterior wall endocardial and epicardial echos and left and right septal endocardial echos and satisfactory measurements of both myocardial thickness and internal diameters. Routine measurements concern end-diastole and end-systole and a shortening ratio (often expressed as an ejection fraction) and a thickening ratio can be derived correctly correlated with cineangiographic estimates.

So a continuous analysis of the rate of change of wall thickness and left ventricular dimensions has been proposed (1, 2, 4). Diastolic changes of short axis diameter are assumed to be related to ventricular filling properties although the left ventricle change of shape prevents satisfactory volume and flow calculations.

The purpose of this work is to analyse simultaneously during diastole and mainly during its rapid filling phase: a) the posterior wall and interventricular septum echograms (including the study of the slope changes); b) the anterior mitral leaflet echogram; c) the internal diameter rate of change. Focus is directed toward the analysis of time relations between the different mechanical events.

#### METHODS AND MATERIAL

The device employed to record the echocardiograms was the Echocardiovisor (Organon Technika) which has conventional single element and multiscan capability. M-mode signals were recorded on a Honeywell linescan recorder. To record the diastolic motion of the anterior mitral leaflet the transducer was aimed toward its free edge and then slightly angulated so that on the same recording could appear septal and posterior wall echograms satisfying the requisites for left ventricular minor axis measurements. The M-mode recordings were always preceded by a dynamic mode observation so that the results of improperly oriented left ventricle (long axis and echo beam angular relationship) could be rejected.

The M-mode recording was placed on a digitizing tablet (Wang Digitizer resolution 0.25 mm) and the selected echos were traced. This was done under the control of a Wang 2200 Calculator (16 K-octets) with a floppy disk unit and a XT plotter (fig. 1). The sampling rate was related to the recording speed (200 per second for a 50 mm per second speed). The following structures were recorded: a) the left and whenever possible right side of the interventricular septum; b) the anterior mitral leaflet; c) the endocardium and epicardium of the left ventricular posterior wall. Each trace was submitted to three conse-



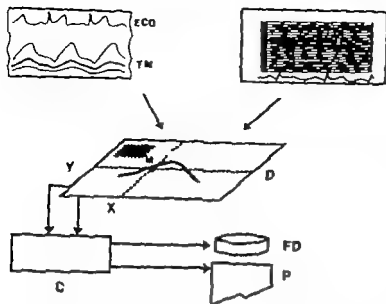


Fig 1 Diagram of the computer-assisted system for M-mode digitizing storage and display (M M-mode recording C Minicomputer FD Floppy disc unit P XY plotter)

cutive readings on the digitizing tablet and the averaged results corrected for scale were stocked on disks without any filtration A three points algo rithm was used for diffe rentiation

These data were computed to derive throughout the cardiac cycle a) the in ternal diameter (D 1) b) the external diameter (D 2) and the averaged mid wall diameter (D 3) c) the rate of change of these diameters d) the inter- ventricular septal thickness, e) the posterior wall thickness f) a charac teristic volume  $W = (D 2/2)^3 - (D 1/2)^3$  related to the myocardial volume

Echocardiograms were obtained from 40 normal subjects 12-35 years old including trained athletes

## RESULTS

An example of results is shown in fig 2 Top left the five traces are plot ted corresponding to septal and posterior wall boundaries and to the anteri or mitral leaflet All recordings are synchronized with the Q Wave of the electrocardiogram Bottom-left the septal and posterior wall thickness and the characteristic volume W are displayed Top-right the instantaneous left ventricular dimensions (external midwall internal diameters) and bottom- right their rate of change (midwall and internal diameters) are displayed The chronology of the different mechanical events are indicated by the bro ken lines the points D E F on the anterior mitral leaflet the change of slope noted I on the posterior wall the change of slope noted J on the in terventricular septum peak lengthening velocity (internal diameter) noted X and its zero crossing Z The sequence D E X I J (Z) F is highly represen- tative of the overall results

These results are summarized in tables I and II In table I the amplitude of different parameters are presented including the shortening diameter ratio the ejection fraction the thickening ratio the endocardial and midwall mean

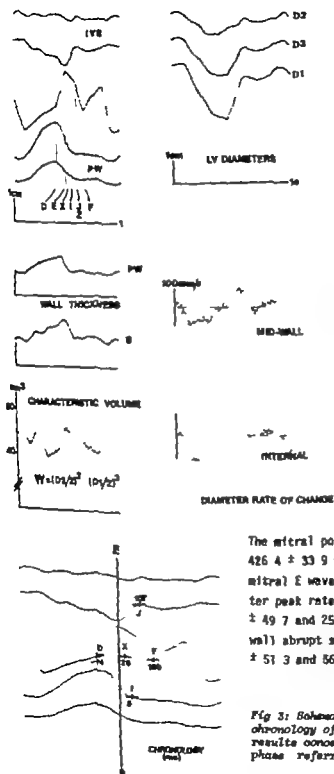


Fig 2: An example of digitized M-mode recordings of posterior wall, interventricular septum, anterior mitral leaflet and derived parameters (see text)-

circumferential fiber shortening rates values in good accordance with the echocardiographic standards and the mean posterior wall thickening rate in good accordance with recent angiographic results (3).

In table II the chronology of the statistically averaged results concerning the rapid filling phase is presented. The results are expressed in two different ways: a) referred to the Q wave of the electrocardiogram; b) referred to the E wave of the anterior mitral leaflet (fig 3).

The mitral point D occurs respectively at  $426.4 \pm 33.9$  ms and  $73.6 \pm 19.3$  ms, the mitral E wave  $500.0 \pm 43.0$  ms, the diameter peak rate of change (point X)  $525.9 \pm 49.7$  and  $25.9 \pm 30.4$  ms, the posterior wall abrupt slope change (point I)  $556.6 \pm 51.3$  and  $56.6 \pm 31.4$  ms, the septal abrupt

Fig 3: Schematic representation of the chronology of the statistically averaged results concerning the rapid filling phase referred to E wave (see text).

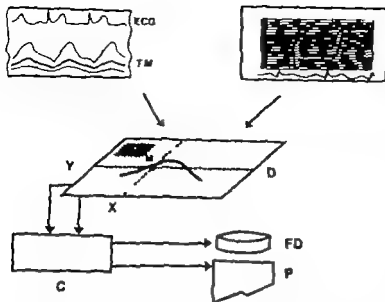


Fig 1 Diagram of the computer-assisted system for M-mode digitizing storage and display (M M-mode recording C Microcomputer FD Floppy disc unit P XY plotter)

cutive readings on the digitizing tablet and the averaged results corrected for scale were stocked on disks without any filtration. A three points algorithm was used for differentiation.

These data were computed to derive throughout the cardiac cycle: a) the internal diameter (D 1), b) the external diameter (D 2) and the averaged mid wall diameter (D 3), c) the rate of change of these diameters, d) the inter-ventricular septal thickness, e) the posterior wall thickness, f) a characteristic volume  $W = (D 2/2)^3 - (D 1/2)^3$  related to the myocardial volume.

Echocardiograms were obtained from 40 normal subjects, 12 - 35 years old, including trained athletes.

## RESULTS

An example of results is shown in fig 2. Top left the five traces are plotted corresponding to septal and posterior wall boundaries and to the anterior mitral leaflet. All recordings are synchronized with the Q Wave of the electrocardiogram. Bottom-left the septal and posterior wall thickness and the characteristic volume  $W$  are displayed. Top right the instantaneous left ventricular dimensions (external, midwall, internal diameters) and bottom-right their rate of change (midwall and internal diameters) are displayed. The chronology of the different mechanical events are indicated by the broken lines: the points D, E, F on the anterior mitral leaflet; the change of slope noted I on the posterior wall; the change of slope noted J on the inter-ventricular septum; peak lengthening velocity (internal diameter) noted X and its zero crossing Z. The sequence D, E, X, I, J, (Z), F is highly representative of the overall results.

These results are summarized in tables I and II. In table I the amplitude of different parameters are presented, including the shortening diameter ratio, the ejection fraction, the thickening ratio, the endocardial and midwall mean

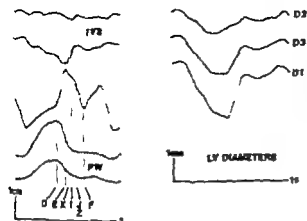
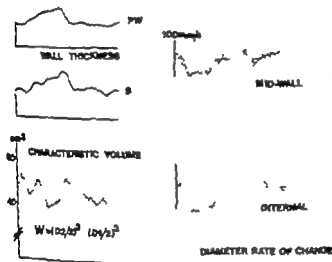


Fig 2 An example of digitized M-mode recordings of posterior wall interventricular septum anterior mitral leaflet and derived parameters (see text).

circumferential fiber shortening rates values in good accordance with the echocardiographic standards and the mean post erior wall thickening rate in good accordance with recent angiographic results (3)

In table II the chronology of the statistically averaged results concerning the rapid filling phase is presented. The results are expressed in two different ways: a) referred to the Q wave of the electrocardiogram; b) referred to the E wave of the anterior mitral leaflet (fig. 3).



The mitral point D occurs respectively at  $426.4 \pm 33.9$  ms and  $73.6 \pm 19.3$  ms the mitral E wave  $500.0 \pm 43.0$  ms the diameter peak rate of change (point X)  $525.9 \pm 49.7$  and  $25.9 \pm 30.4$  ms the posterior wall abrupt slope change (point J)  $556.6 \pm 51.3$  and  $56.6 \pm 31.4$  ms the septal abrupt

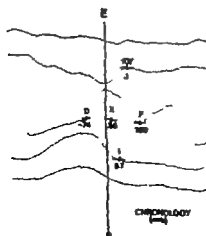


Fig 3: Schematic representation of the chronology of the statistically averaged results concerning the rapid filling phase referred to E wave (see text)

TABLE I Amplitude results and derived parameters

## LEFT VENTRICLE

End diastolic diameter	47.3	$\pm$	8.2	mm
End systolic diameter	33.2	$\pm$	6.7	mm
Shortening ratio	29	$\pm$	07	
Ejection fraction	67	$\pm$	08	

## POSTERIOR WALL

End diastolic thickness	7.0	$\pm$	1.9	mm
End-systolic thickness	11.4	$\pm$	3.6	mm
Thickening ratio	1.67	$\pm$	45	

## MEAN CIRCUMFERENTIAL FIBER SHORTENING RATE

Endocardial	1.57	circ/s
Mid wall	73	circ/s

## THICKENING RATE

Posterior wall	1.95	thickness/s
----------------	------	-------------

TABLE II Chronology of the mechanical events occurring during the rapid filling phase (milliseconds)

REFERENCE	Q wave	E wave
Point D (anterior mitral leaflet)	426.4 $\pm$ 33.9	73.6 $\pm$ 19.3
Point E (anterior mitral leaflet)	500.0 $\pm$ 43.0	
Point X (peak lengthening velocity)	525.8 $\pm$ 49.7	25.9 $\pm$ 30.4
Point I (posterior wall)	556.6 $\pm$ 51.3	56.6 $\pm$ 31.4
Point J (interventricular septum)	606.6 $\pm$ 43.6	106.6 $\pm$ 32.9
Point F (anterior mitral leaflet)	650.0 $\pm$ 49.4	150.0 $\pm$ 27.9

slope change (point J)  $606.6 \pm 3.6$  and  $106.6 \pm 32.9$  ms the mitral point F  $650.0 \pm 49.4$  and  $150.0 \pm 27.9$  ms. The end of rapid filling derived from the internal diameter can be evaluated only from long diastole. Its occurrence then derived from its rate of change zero-crossing Z is synchronous with J. Occasionally the diameter then decreases until the point F.

The pattern of the posterior wall thickness variations during the cardiac cycle is well known though its description during the filling phase remains poorly detailed. We found a similar pattern for the interventricular pattern but with a slight asynchronism. The three filling phases (rapid slow atrial contraction) are clearly demonstrated on the internal diameter curve. In spite of the incompressibility of the myocardium the characteristic volume V showed a 10 % minimal scatter due to various factors discussed below.

### DISCUSSION

Cineangiographic studies demonstrate variable eccentricity of the left ventricle (variable axis ratio in an ellipsoidal or truncated ellipsoidal model) throughout cardiac cycle. Mitral flow therefore cannot be derived from diastolic continuous diameter rate of change. However if the rate of change of the axis ratio exhibit small temporal gradients internal ventricular volume and diameter time variations may be highly correlated.

The successful simultaneous recording of mitral flow and cusps motion in animal experiments has permitted to examine their dynamic relations (5).

Our findings locating peak velocity of short axis lengthening  $25.9 \pm 30.4$  after the echographic E wave are in good accordance with transmitral flow measurements and enhance the reliability of echographic measurements (no phase disturbance).

It is commonly admitted and found in most published examples of simultaneously recorded transmitral and anterior mitral leaflet echogram that flow is still positive at F point. Our findings could lead to different conclusions. If a sufficient diastolic duration is present diameter lengthening rate of change do cross zero line before (45 ms) F point and occasionally becomes negative at F point. Indeed we were able to collect examples of transmitral flow with long diastoles and traces demonstrate zero flow around the echographic F point (5). Contradiction is therefore avoided. It must not be concluded that effective mitral flow is null both transmitral flow and diameter variations referring to a total annular flow. Our examples with short diastolic duration show positive diameter variations. It is concluded that

graphic internal left ventricular diameter and transatrial flow are highly correlated as long as time is considered

The abrupt slope change observed on the endocardial echo of the left ventricular posterior wall precedes significantly the end of the rapid filling phase ( $50.0 \pm 29.6$  ms) and F point ( $93.4 \pm 32.8$  ms) the diameter increase in its terminal phase is related to septal motion. An abrupt change of slope is in turn observed on the septal echogram this time coinciding with the end of the rapid filling phase ( $43.4 \pm 37.3$  before F point). The significance of this echographic asynchronism of the left ventricular walls motion is not clear due either to ventricular motion as a whole or to local phenomena.

The opportunity to follow simultaneously the right side of the interventricular septum and the epicardial border of the posterior wall allows the computation of the left ventricular external diameter. It seems interesting for physiological purposes to consider the averaged value of internal and external diameters defined as mid wall diameter in the site where the circumferential fibers are located anatomically (6).

The value of such computation depends on its entry date parameters. The improved quality of the echocardiogram does not prevent ambiguity in path selection when a given boundary has to be read. A first possible test consists in an analysis of the thickening and thinning patterns of myocardial walls which prevents major errors but a second test based on the myocardial volume constancy seems available and of greater interest. This property is used with angiographic method to calculate the thickness variations of the left ventricular wall. The inaccuracy of the end systolic wall thickness prevent a direct evaluation (computation of the myocardial volume with end systolic data would give a result with considerable excess in the expected value).

With echocardiography the wall thickness is measured with similar accuracy throughout the cardiac cycle. To include the term myocardial volume constancy we have calculated the characteristic volume parameter  $W = (D/2)^3$

$(D/2)^3$  Computation of left ventricular internal volume with angiography demonstrate a continual variation in the degree of ellipsoidal eccentricity related to the smaller variations of the long axis compared with the short axis.  $W$  dependant of the axis ratio must show a significant (but of limited amplitude) end systolic decrease. Observed variations are related to superimposition of these variations and reading errors concerning the selec

ted boundaries. A continuous analysis of the axis ratio by cineangiographic method would contribute to the applicability and interest of the test.

#### ACKNOWLEDGEMENTS

This work was supported by a grant from the Délégation Générale à la Recherche Scientifique et Technique (A C C Biologie et Fonction du Myocarde).

#### REFERENCES

1. BROWER B W, VAN DORP W G, VOGEL J A, ROELANDT J R. An improved method for the quantitative analysis of the M-mode echocardiograms. *Eur J Cardiol* 3 171 1975.
2. GIBSON D G, BROWNE D. Measurements of instantaneous left ventricular dimensions and filling rate in man using echocardiography. *Brit Heart J* 35 1141 1973.
3. GOULD L K, KENNEDY W J, FRIMER M, POLLACK G H, DODGE H T. Analysis of wall dynamics and directional components of left ventricular contraction in man. *Amer J Cardiol* 38 322 1976.
4. GRIFFITH J M, HENRY W J. Video scanner-analog computer system for semi-automatic analysis of routine echocardiograms. *Amer J Cardiol* 32 961 1973.
5. LAHADO S, YELLIN E L. Simultaneous recordings of mitral valve echogram and transmitral flow. In *The Mitral Valve* 155. E Arnold London 1975.
6. STREETER, D D, HARRIS, W T. Engineering mechanics for successive states in canine left ventricular myocardium. II. Fiber angle and sarcomere length. *Circulat Res* 33 656 1973.





# Acta Medica Scandinavica

Supplementum 628

## Negative Consequences of Blood Pressure Reduction

*Proceedings of a Symposium at Foresta, Stockholm, Sweden,  
on June 2, 1978*

Edited by Lennart Hansson and Matts Henning



# Acta Medica Scandinavica

Supplementum 628

## Negative Consequences of Blood Pressure Reduction

*Proceedings of a Symposium at Foresta, Stockholm, Sweden,  
on June 2, 1978*

Edited by Lennart Hansson and Matts Henning

# Acta Medica

originally published as *Nordiskt Medicinskt Arkiv* was founded in 1869 by Professor Axel Key MD. In 1901 (from volume 34) this journal was divided into a medical and a surgical section. Since 1919 (from volume 52) the medical section has been published under the name of *Acta Medica Scandinavica*.

## *Acta Medica Scandinavica*

publishes papers on general medicine mainly from Denmark, Finland, Iceland, Norway, Sweden and the Netherlands. Short preliminary reports (not exceeding two pages) will be published at short notice. The papers are published in English, French or German. *Acta Medica Scandinavica* is published on a non-profit basis.

## *Subscriptions*

to *Acta Medica Scandinavica* (two volumes of six numbers each annually) include free supplements to the current volumes.

## *Subscription Rates*

Per annum = two volumes  
In Denmark, Finland, Iceland, Norway, Sweden and the Netherlands: Sw. cr. 330 incl. postage. Swedish subscribers add VAT.  
Other countries: Sw. cr. 375 incl. postage.

## *Chief Editor*

Professor Jan G. Waldenström, MD  
*Acta Medica Scandinavica*  
Kungsgatan 54  
S-111 35 Stockholm, Sweden

## *Editorial Office*

*Acta Medica Scandinavica*  
Kungsgatan 54  
S-111 35 Stockholm, Sweden  
(All correspondence concerning manuscripts and editorial matters)  
Telephone 08/21 77 63

## *Subscription, Distribution and Advertising*

The Almqvist & Wiksell Periodical Company  
Gamla Brogatan 26, Box 62  
S-101 20 Stockholm 1, Sweden

## *Printers*

Almqvist & Wiksell Tryckeri AB  
S-751 81 Uppsala, Sweden

# Negative Consequences of Blood Pressure Reduction

*Proceedings of a Symposium at Foresta, Stockholm, Sweden,  
on June 2 1978*

Edited by Lennart Hansson and Matts Henning

# Acta Medica

originally published as *Nordiskt Medicinskt Arkiv* was founded in 1869 by Professor Axel Key MD. In 1901 (from volume 34) this journal was divided into a medical and a surgical section. Since 1919 (from volume 52) the medical section has been published under the name of *Acta Medica Scandinavica*.

## *Acta Medica Scandinavica*

publishes papers on general medicine mainly from Denmark, Finland, Iceland, Norway, Sweden and the Netherlands. Short preliminary reports (not exceeding two pages) will be published at short notice. The papers are published in English, French or German. *Acta Medica Scandinavica* is published on a non-profit basis.

## *Chief Editor*

Professor Jan G. Waldenström MD  
*Acta Medica Scandinavica*  
Kungsgatan 54  
S-111 35 Stockholm, Sweden

## *Editorial Office*

*Acta Medica Scandinavica*  
Kungsgatan 54  
S-111 35 Stockholm, Sweden  
(All correspondence concerning  
manuscripts and editorial matters)  
Telephone 08/21 77 63

## *Subscriptions*

to *Acta Medica Scandinavica* (two volumes of six numbers each annually) include free supplements to the current volumes.

## *Subscription Rates*

Per annum = two volumes.  
In Denmark, Finland, Iceland, Norway, Sweden and the Netherlands: Sw. cr 330 incl. postage. Swedish subscribers add VAT.  
Other countries: Sw. cr 375 incl. postage.

## *Subscription, Distribution and Advertising*

The Almqvist & Wiksell Periodical Company  
Gamla Brogatan 26, Box 62  
S-101 20 Stockholm 1, Sweden

## *Printers*

Almqvist & Wiksell Tryckeri AB  
S-751 81 Uppsala, Sweden

# CONTENTS

## Introduction

*Leifert Hansson, Mats Henning*

## Negative consequences of blood pressure reduction

*Leifert Hansson*

## Negative consequences of reduction of blood pressure – central circulatory aspects

*Rune Sannerstedt*

## Effect of blood pressure reduction on tissue perfusion

*Ramon Sverrisdottir*

## Arterial hypotension and its consequences for the cerebral circulation

*Leifert Hansson*

## Discussion

## Antihypertensive drug reactions from different organ systems and functions – an introduction

*Mats Henning*

## Adverse reactions to antihypertensive drugs, reported to the Swedish Adverse Drug Reaction Centre

*Göran Boman*

## Registration of side effects by means of a questionnaire

*Ove Andersson*

## Discussion

## Adverse reactions to antihypertensive drug therapy central nervous system

*Mats Henning*

## Vasospastic phenomena in patients with beta-adrenoceptor blocking agents

*Kersti Ekesson, Lars-Eric Larss, Kerstin Sandqvist*

## Kidney damage induced by antihypertensive treatment

*Hel C. Hasselgren*

## Respiratory aspects

*Göran Boman*

## Discussion

## Liver damage due to antihypertensive drugs

*Rolf Olsson*

## Discussion





## INTRODUCTION

Reduction of elevated arterial pressure is known to reduce both morbidity and mortality due to cardiovascular causes in hypertensive patients. For these reasons antihypertensive therapy is generally accepted and the beneficial effects of such treatment are frequently quoted in the literature whereas negative consequences of lowered blood pressure including side effects from antihypertensive therapy attract considerably less interest.

In our opinion these aspects of blood pressure lowering therapy also require attention. Hence, we invited clinically oriented researchers to give brief summaries of the negative effects of blood pressure reduction as such, e.g. as regards the cerebral circulation, and also side effects from antihypertensive drugs affecting various organs or organ systems. These presentations were given at a conference held on June 2nd 1978 in Forssa, Stockholm.

In order to balance the negative effects of blood pressure lowering treatment reported during the meeting against its undisputable beneficial effects of such therapy a panel discussion on the risk-benefit aspect concluded the meeting.

This supplement contains nearly all the presentations given as well as excerpts of the discussion and a summary of the panel discussion, the purpose being to make a compiled information available to a wider range of clinicians than those present at the conference.

As organizers of the conference and as editors of this supplement we wish to express our sincere gratitude to CIBA-GEIGY Pharmaceuticals Division of Sweden and Anders Lindqvist who made it possible to arrange the meeting and to publish the proceedings.

*Lennart Hansson*

*Ulf Hjemming*

The effect of sympathetic inhibition on plasma levels of catecholamines, growth hormone, glucocorticoids and cortisol

*Bengt Göran Hansson, Berni Håkfeldt*

Effect of antihypertensive therapy on electrolytes

*Jan Castenfors*

Impairment of glucose metabolism during treatment with antihypertensive drugs

*Calle Bengtsson*

Discussion

Elevated serum uric acid levels during treatment with antihypertensive drugs

*Calle Bengtsson*

Hematological side effects from antihypertensive drugs

*Bengt Lundh, Karl H. Hasselgren*

Discussion

Cutaneous side effects from beta-blockers and other antihypertensive agents

*Håkan Mölbacken*

Discussion

Systemic blood pressure and the eye

*Albert Alm*

Discussion

Immunological side-effects of antihypertensive drugs

*Göran Holm*

Serum lipid changes during treatment with antihypertensive drugs

*Stephan Rössner*

Discussion

Negative consequences of reduction of blood pressure – influence on sexual function

*Rune Sannerstedt*

Discussion

Fetal effects of antihypertensive drugs

*Per Lundborg*

Discussion

Treatment of hypertension – risk/benefit, excerpts of a panel discussion

*Chairman and referee: Hans Dunder*

*Panel members: Lennart Hansson, Mats Henning, Rune Sannerstedt, Hans Åberg*

## INTRODUCTION

Reduction of elevated arterial pressure is known to reduce both morbidity and mortality due to cardiovascular diseases in hypertensive patients. For these reasons antihypertensive therapy is generally accepted and the beneficial effects of such treatment are frequently quoted in the literature whereas negative consequences of lowered blood pressure including side effects from antihypertensive therapy attract considerably less interest.

In our opinion these aspects of blood pressure lowering therapy also require attention. Hence, we invited clinically oriented researchers to give brief summaries of the negative effects of blood pressure reduction as such, e.g. as regards the cerebral circulation, and also side effects from antihypertensive drugs affecting various organs or organ systems. These presentations were given at a conference held on June 2nd, 1978 in Forsta, Stockholm.

In order to balance the negative effects of blood pressure lowering treatment reported during the meeting against its undisputable beneficial effects of such therapy a panel discussion on the risk-benefit aspect concluded the meeting.

This supplement contains nearly all the presentations given as well as excerpts of the discussion and a summary of the panel discussion, the purpose being to make a compiled information available to a wider range of clinicians than those present at the conference.

As organizers of the conference and as editors of this supplement we wish to express our sincere gratitude to CIBA-GEIGY Pharmaceuticals Division of Sweden and Anders Lindqvist who made it possible to arrange the meeting and to publish the proceedings.

Lennart Hansson

Matts Henning



# NEGATIVE CONSEQUENCES OF BLOOD PRESSURE REDUCTION

Leomar Hansson

## INTRODUCTION

The beneficial effects of blood pressure reduction in hypertensive patients have gained general acceptance during the last two or three decades mainly due to the fact that reduced morbidity and mortality can be demonstrated when such therapy is instituted (Veterans Administration 1967; Veterans Administration 1970; Berglund et al. 1978).

It is also well known that all forms of pharmacological treatment will cause not only the therapeutic effect but also adverse effects (Netter 1976).

Regarding the balance between the therapeutic effect and the adverse effects it is also quite obvious that the safety of any particular compound has to be related to the efficacy of the drug, to the seriousness of the disease to be treated and to other available therapies (Liljestrand 1976).

In consequence, this benefit-risk ratio would not be constant for any certain drug but will vary with time. Since the purpose of this symposium is to evaluate the benefit-risk ratio for antihypertensive therapy with a strong emphasis on the risk side, a list of possible effects of drug treatment is given in Table I.

The definition of a side effect as been given as: any response to a drug that is noxious and unintended and that occurs at doses used in man for prophylactic diagnosis or therapy excluding failure to produce the intended purpose (Karch & Leisner 1975). As can be seen, the list in Table I does not completely adhere to this definition. It is debatable whether an exaggeration of the therapeutic effect should be listed as a side effect, although it certainly can be regarded as an unwanted effect.

## ANTIHYPERTENSIVE THERAPY

### *Exaggeration of the therapeutic effect*

Clearly antihypertensive therapy occasionally causes a pronounced reduction of arterial pressure thereby

leading to complications as regards the central circulation, the peripheral circulation and maybe having its most drastic effects on the cerebral circulation. These aspects will be dealt with more in detail in the following three papers.

### *Side effects*

Toxic effects are experienced rarely with antihypertensive agents. As an example can be mentioned some forms of liver damage during treatment with alpha-methyl dopa.

*Drug allergy* is caused either by the drug itself or by a combination of the drug with protein (or a drug metabolite and protein) which forms an antigen that precipitates an allergic reaction. It is conceivable that the "practolol syndrome" and the hydralazine syndrome are caused by this mechanism.

Since many if not all of the listed adverse effects in Table I will be dealt with more in detail during the symposium a final comment should only be made as regards the rebound effect. In reference to currently used antihypertensive agents clonidine is of particular

Table I Possible effects of pharmacotherapy

- |                                       |
|---------------------------------------|
| A. Therapeutic effect                 |
| B. Adverse effects                    |
| a. Exaggeration of therapeutic effect |
| b. Side effects                       |
| toxic effects                         |
| drug allergy                          |
| idiosyncrasy                          |
| - drug interaction                    |
| carcinogenicity                       |
| drug dependence                       |
| mutagenicity                          |
| thermogenicity                        |
| pseudo side effects                   |
| c. Rebound effects                    |

interest since this drug may cause a rapid and serious rise of blood pressure if treatment is stopped abruptly (Hansson et al 1973).

Finally in this brief analysis of unwanted effects of pharmacotherapy therapeutic failure has not been

included. Obviously therapeutic failure can be due to either absolute or relative underdosage. However this should not in my opinion be considered as a side effect although some authors have chosen to include also therapeutic failure in listings of side effects.

## REFERENCES

- Berglund G, Wilhelmson L, Sinnerstedt R, Hansson L, Andersson O, Sverrisson R, Wedel H C & Wikstrand J. Coronary heart-disease after treatment of hypertension. *Lancet* 1: 1-4, 1978.
- Hansson L, Hunyor S N, Julius S & Hoobler S W. Blood pressure crisis following withdrawal of clonidine (Catapres, Catapresan), with special reference to arterial and urinary catecholamine levels, and suggestions for acute management. *Am Heart J* 85: 605-610, 1973.
- Karch F E & Lesagna L. Adverse drug reactions. A critical review. *JAMA* 234: 1236-1241, 1975.
- Liljestrand Å. Pathogenesis and significance of adverse drug reactions: Importance to drug regulatory agencies. In: *Clinical Pharmacological Evaluation in Drug Control* WHO Symposium in Deidesheim, pp 78-81, 1976.
- Netter K J. Pathogenic mechanisms of adverse drug reactions. In: *Clinical Pharmacological Evaluation in Drug Control* WHO Symposium in Deidesheim, pp 62-66, 1976.
- Veterans administration cooperative study group on antihypertensive agents: Effects of treatment on morbidity in hypertension. *JAMA* 202: 1028-1034, 1967.
- Veterans administration cooperative study group on antihypertensive agents: Effects of treatment on morbidity in hypertension. *JAMA* 213: 1143-1152, 1970.

## NEGATIVE CONSEQUENCES OF REDUCTION OF BLOOD PRESSURE - CENTRAL CIRCULATORY ASPECTS

Rune Sannerstedt

Antihypertensive drugs influence the circulatory system in various ways, apart from their therapeutic hypotensive action. The body's response to these, usually unwanted effects will vary depending on such factors as

- 1) the type of substance
- 2) the dose given
- 3) the length of treatment
- 4) the severity and nature of the hypertensive disease
- 5) the individual's posture and level of mental and physical activity
- 6) other concomitant medication

### INFLUENCE ON REGULATION OF BLOOD PRESSURE

*Postural hypotension* due to sudden changes of posture or to the individual standing still for long periods is common, today particularly during treatment with postganglionic sympathetic inhibitors, e.g. bethanidine and guanethidine. It is mainly caused by reduced venous return, leading to pooling of blood in, above all, the lower extremities, and leads to objective symptoms in the form of dizziness and, in severe cases, fainting attacks. Postural hypotension may also occasionally occur during treatment with other drugs with an inhibitory effect on the sympathetic nervous system as well as during diuretic therapy, not least in geriatric patients with impaired homeostatic regulatory mechanisms owing to e.g. age-related changes in baroreceptor function.

Severe postural reactions and prolonged fainting have also been reported after use of the alpha-adrenoceptor blocker prazosin (not registered in Sweden), especially when too high doses are given initially leading to the "first-dose phenomenon".

Hypotension during physical exertion may occur during treatment with postganglionic sympathetic inhibitors, such as bethanidine and guanethidine, with a

fall of blood pressure instead of the normal rise. This may manifest itself in the form of excessive tiredness and the fall of blood pressure may occasionally be so great that the patient faints, for example when cycling.

*Paradoxical hypertension* may occur during treatment with certain antihypertensive drugs and in severe cases may lead to hypertensive crises with hypertensive encephalopathy of varying severity. An example is clonidine, which may cause an acute catecholamine effect, leading to a hypertensive crisis, if withdrawn abruptly. Parenteral administration of sympathetic inhibitors, such as bethanidine, guanethidine and methyldopa, usually causes a transient moderate rise of blood pressure initially. In patients with pheochromocytoma, however, they may provoke a considerable blood pressure rise by increasing the sensitivity of the blood vessels to circulating catecholamines.

### INFLUENCE ON THE CONDUCTION SYSTEM

All antihypertensive drugs with an inhibitory effect on the sympathetic nervous system have, in principle, a negative chronotropic action, leading to bradycardia. As a rule, this effect is of no clinical importance except during treatment with  $\beta$ -adrenoceptor blockers, which sometimes cause excessive sinus bradycardia. Heart rate as low as 5-10 beats per minute has been reported. For the other sympathetic inhibitors, such as bethanidine, guanethidine, clonidine, methyldopa and reserpine, this risk is generally negligible at therapeutic dose level.

Peripheral vasodilators, such as hydralazine and minoxidil (which is not registered in Sweden), have a positive chronotropic action and frequently cause tachycardia. This tendency may be regarded as a compensatory reflex mechanism aimed at increasing the heart rate, and thus the cardiac output, in order to



counteract the blood pressure fall resulting from peripheral vasodilatation. A characteristic feature of the  $\beta$ -adrenoceptor blockers is their *negative dromotropic effect*. In predisposed individuals the reduced conduction velocity may lead to atrioventricular block of varying degree.

Owing to their tendency to induce hypokalaemia, the diuretics could have a *positive bathmotropic effect* i.e. they increase the excitability of the myocardium, with a consequent risk of ectopic beats and tachyarrhythmias.

### INFLUENCE ON THE MYOCARDIUM

Another characteristic feature of the  $\beta$ -adrenoceptor blockers, seen as a group is their *negative inotropic effect* leading to reduction of the contractile force of the myocardium. In predisposed patients this effect may lead to cardiac decompensation, which in early phases may present as a gradually increasing, radiologically demonstrable, cardiac volume. Treatment with ganglion blockers or postganglionic sympathetic inhibitors, such as bethanidine and guanethidine, may lead to a *reduced oxygen supply* to the myocardium and coronary ischaemia. The reduced oxygen supply is a result of reduced cardiac output and consequent reduced coronary blood flow. Clinically this may result in angina pectoris. Cases of sudden death during the night due to myocardial infarction, have also been attributed to drug induced hypotension. The previously mentioned positive chronotropic effect of the peripheral vasodilators e.g. hydralazines, often leads to an overall *increase in cardiac work*. This may lead to a relative myocardial ischaemia, which in predisposed patients may manifest itself as angina pectoris.

### INFLUENCE ON BLOOD VOLUME

Theoretically all drugs with an inhibitory action on the sympathetic nervous system are liable to cause *hyperkalaemia* i.e. an increase in the volume of circulating blood. This effect is particularly marked during treatment with postganglionic sympathetic inhibitors such as guanethidine but also occurs with for example, methyldopa and clonidine. Fluid retention may also occur during treatment with some of the peripheral vasodilators. Thus, guanacydine and minox

idil neither of which is registered in Sweden, tend to cause massive fluid retention. Clinically the hyperkalaemia leads to development of resistance to the drug and the patient may observe a slight to moderate weight gain. In more severe cases decline oedema may occur and predisposed patients may develop cardiac decompensation.

Excessive diuretic therapy may lead to *hypovolaemia* leading to a marked fall of blood pressure and postural reactions. In elderly patients, particularly continued treatment may result in shock-like states.

### INFLUENCE ON THE PULMONARY CIRCULATION

*Increased pulmonary blood volume* with pulmonary stasis, possibly progressing to manifest left heart failure and pulmonary oedema, may be expected in connection with hypervolaemia induced by sympathetic inhibitors.

Pulmonary congestion and related secondary pulmonary effects may explain the bizarre symptoms formerly seen during treatment with ganglion blockers. The syndrome was particularly common during treatment with hexamethonium and was therefore known as "hexamethonium lung".

*Increased blood pressure in the pulmonary artery* has been reported during treatment with peripheral vasodilators, e.g. minoxidil. The underlying mechanism for this pressure rise remains unclear.

### FINAL COMMENT

Detailed descriptions of the negative effects on the circulatory system of antihypertensive drugs have been given in recently published monographs (Burk 1977 Gross 1977 Tester Dalderup 1977). The multiplicity of these adverse effects, together with the facts that they often have a decisive influence on the therapeutic response, may represent a major problem during practical management of hypertensive patients.

A good knowledge of these points on the part of the doctor markedly improves the chances of achieving optimal blood pressure control with a minimum of subjective and objective unwanted effects and side effects from the circulatory system.

## REFERENCES

- Bourke E J. Diuretic drugs. In: Side effects of drugs annual I, pp 180-189. Ed. M N G Duker. Excerpta Medica. Amsterdam - Oxford 1977
- Geiss F (ed): Handbook of experimental pharmacology: Antihypertensive agents. Springer-Verlag, Berlin, Heidelberg, New York 1977
- Tetter-Dalderup C B M. Hypotensive drugs. In: Side effects of drugs annual I, pp 164-179. Ed. M N G Duker. Excerpta Medica. Amsterdam - Oxford 1977

counteract the blood pressure fall resulting from peripheral vasodilatation. A characteristic feature of the  $\beta$ -adrenoceptor blockers is their *negative dromotropic effect*. In predisposed individuals the reduced conduction velocity may lead to atrioventricular block of varying degree.

Owing to their tendency to induce hypokalaemia, the diuretics could have a *positive bathmotropic effect* i.e. they increase the excitability of the myocardium, with a consequent risk of ectopic beats and tachyarrhythmias.

### INFLUENCE ON THE MYOCARDIUM

Another characteristic feature of the  $\beta$ -adrenoceptor blockers, seen as a group is their *negative inotropic effect* leading to reduction of the contractile force of the myocardium. In predisposed patients this effect may lead to cardiac decompensation, which in early phases may present as a gradually increasing, radiologically demonstrable, cardiac volume. Treatment with ganglion blockers or postganglionic sympathetic inhibitors, such as bethanidine and guanethidine may lead to a *reduced oxygen supply* to the myocardium and coronary ischaemia. The reduced oxygen supply is a result of reduced cardiac output and consequent reduced coronary blood flow. Clinically this may result in angina pectoris. Cases of sudden death during the night due to myocardial infarction, have also been attributed to drug induced hypotension. The previously mentioned positive chronotropic effect of the peripheral vasodilators, e.g. hydralazines, often leads to an overall *increase in cardiac work*. This may lead to a relative myocardial ischaemia, which in predisposed patients may manifest itself as angina pectoris.

### INFLUENCE ON BLOOD VOLUME

Theoretically all drugs with an inhibitory action on the sympathetic nervous system are liable to cause *hypovolaemia* i.e. an increase in the volume of circulating blood. This effect is particularly marked during treatment with postganglionic sympathetic inhibitors, such as guanethidine, but also occurs with for example methyldopa and clonidine. Fluid retention may also occur during treatment with some of the peripheral vasodilators. Thus, guanacydine and minox

idil neither of which is registered in Sweden, tend to cause massive fluid retention. Clinically the hypovolaemia leads to development of resistance to the drug and the patient may observe a slight to moderate weight gain. In more severe cases decline oedema may occur and predisposed patients may develop cardiac decompensation.

Excessive diuretic therapy may lead to *hypovolaemia* leading to a marked fall of blood pressure and postural reactions. In elderly patients, particularly continued treatment may result in shock-like states.

### INFLUENCE ON THE PULMONARY CIRCULATION

*Increased pulmonary blood volume* with pulmonary stasis, possibly progressing to manifest left heart failure and pulmonary oedema, may be expected in connection with hypervolaemia induced by sympathetic inhibitors.

Pulmonary congestion and related secondary pulmonary effects may explain the bizarre symptoms formerly seen during treatment with ganglion blockers. The syndrome was particularly common during treatment with hexamethonium and was therefore known as "hexamethonium lung".

*Increased blood pressure in the pulmonary artery* has been reported during treatment with peripheral vasodilators, e.g. minoxidil. The underlying mechanism for this pressure rise remains unclear.

### FINAL COMMENT

Detailed descriptions of the negative effects on the circulatory system of antihypertensive drugs have been given in recently published monographs (Buurke 1977, Gross 1977, Tester-Dalderup 1977). The multiplicity of these adverse effects, together with the facts that they often have a decisive influence on the therapeutic response, may represent a major problem during practical management of hypertensive patients.

A good knowledge of these points on the part of the doctor markedly improves the chances of achieving optimal blood pressure control with a minimum of subjective and objective unwanted effects and side effects from the circulatory system.

# EFFECT OF BLOOD PRESSURE REDUCTION ON TISSUE PERFUSION

Ramon Sniersson

## INTRODUCTION

The blood-flow in a tissue is determined by the perfusion pressure (arterial blood pressure minus venous blood pressure) and blood-flow resistance in the tissue according to the equation:

$$\text{Blood-flow} = \frac{\text{perfusion pressure}}{\text{resistance}}$$

From this equation follows that blood-flow will decrease when the perfusion pressure falls if resistance is unchanged. This is illustrated in Figure 1 which shows the effect of acute blood pressure reduction on hand blood-flow under maximal vasodilatation of the hand blood vessels.

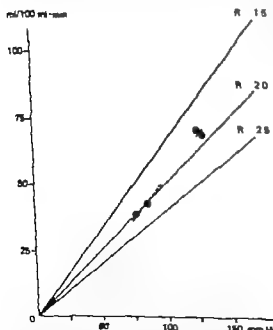


Figure 1 Hand blood-flow under maximal vasodilatation and mean blood pressure at a hypertensive patient, in whom an acute blood pressure reduction was induced by 1) intrathecal infusion. Resistance lines are given and R represents blood-flow resistance in relative units.

## AUTOREGULATION OF BLOOD-FLOW

Under normal conditions, vascular resistance does not remain unchanged when blood pressure is reduced. Most tissues show some degree of autoregulation and in these tissues the resistance vessels compensate more or less completely for the blood pressure reduction by dilatation. This regulation has been ascribed to: a) an accumulation of vasodilating metabolites when blood flow tends to go down, b) a direct effect of the blood pressure on the vascular smooth muscle activity. By distending the small vessels and thus stretching the smooth muscle cells in the wall the blood pressure stimulates these cells to contraction. When the blood pressure falls and the tension in the smooth muscle cells is decreased, the activity in these cells is reduced, which causes the blood vessels to dilate compensatorily (Folchow 1964).

The degree of blood-flow autoregulation differs from one tissue to another. The autoregulation is most pronounced in tissues where the blood vessels are regulated mostly by local factors and in which the vasomotor nerves are of minor importance for the regulation of flow. It is best developed in vital organs, such as the brain, the kidneys (Figure 2), the intestines and the heart (Folchow & Neil 1971). Concerning the heart and the coronary circulation the situation is, however, somewhat more complex since blood pressure reduction also reduces the oxygen consumption and the metabolic need of the heart muscle. The skeletal muscles show a moderate degree of autoregulation. The skin blood vessels are mainly governed by the vasomotor nerves and show very little autoregulation.

It can thus be summarized that in tissues with pronounced autoregulation the blood-flow remains unchanged or almost unchanged until the blood pressure reaches such a low value that the capacity of the regulatory mechanism is exhausted. Below this lower



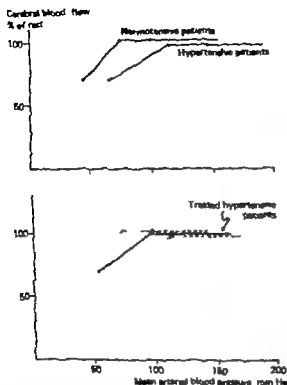


Figure 3 The upper panel shows mean curves of relating cerebral blood-flow to blood pressure in normotensive and severely hypertensive subjects. The lower panel represents another group of patients while a formerly severe hypertension, which at the time of the study was effectively controlled by antihypertensive therapy. From Somerville 1976. By permission.

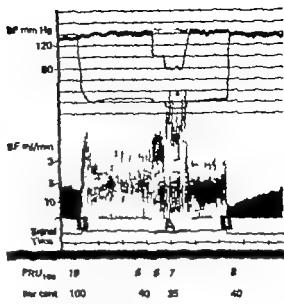


Figure 4 Effect of an experimental femoral artery occlusion on the hand-forearm blood-flow in the cat. Observe that blood-flow (BF) is recorded with drop recorder technique, which means that flow is inversely proportional to the height of the curve. Mean blood pressure (BP) is given proximal to ("systemic pressure") as well as distal to the occlusion ("local perfusion pressure"). The figures at the bottom show vascular resistance in the hand-forearm (in relative units and per cent). Note the autoregulatory change in resistance when the artery occlusion is applied (?). When the "local perfusion pressure" distal is further reduced at A as a consequence of a "systemic pressure" reduction, blood-flow goes down and resistance remains unchanged, since the capacity for autoregulation is already used up. From Thomsen 1962. By permission.

## CLINICAL ASPECTS ON BLOOD PRESSURE REDUCTION

at a higher systemic blood pressure than normal (Figure 4).

Finally tissue blood-flow may be influenced by changes at cellular level in the resistance vessels induced by drugs permissive therapy either by baroreceptor activation or by direct effects of the drug on the smooth muscle cells. For example,  $\beta$ -blockers are known to increase smooth muscle tone in the resistance vessels (Figure 5). Such an increase in vascular tone reduces resting blood-flow at normal perfusion pressure, but blood-flow under haemia or hypotension may also be affected at least in tissues where vasomotor nerves dominate the regulation of the blood-flow and where local factors are less important.

The effects of blood pressure reduction on cerebral blood-flow are well known and will be dealt with elsewhere in these proceedings (Hazzam 1978).

Concerning myocardial blood-flow a reduction of the systemic blood pressure implies not only a reduced perfusion pressure for the coronary vascular bed, but also a reduced work load and reduced oxygen need for the heart muscle. When  $\beta$ -blockers are used for the blood pressure treatment, the oxygen need is further reduced due to the reduction in heart rate. For this reason the need for a fully maintained coronary flow does not exist and an aggravation of angina pectoris symptoms due to blood pressure lowering therapy is therefore uncommon with modern drugs.

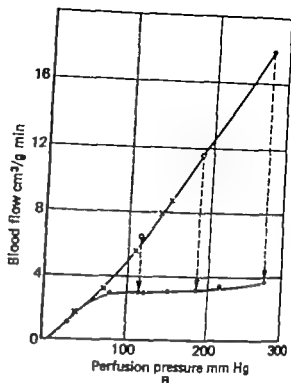
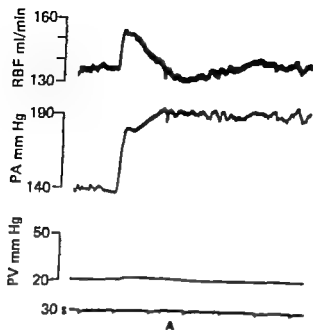


Figure 2. Acute (O-O) and long-term (●-●) effect of blood pressure change on renal blood-flow. From Scrupé & D. Wardener 1949 (A), and Thurau & Kramer 1959 (B). By permission

limit for the autoregulation the blood-flow falls in parallel with the blood pressure. In tissues with less pronounced autoregulation the blood flow falls more or less in pace with the pressure drop over the whole pressure range.

#### BARORECEPTORACTIVATION AND BLOOD-FLOW

A blood pressure drop induces via the baroreceptors in the carotid sinus and the aortic arch an enhanced vasomotor nerve outflow to various vascular beds: resistance vessels (arteries and arterioles) as well as capacitance vessels (veins). Resistance vessels with a dominating local regulation are less affected than vessels which are strongly regulated by the nerves. During long term blood pressure change the baroreceptors "reset" to the new pressure level (Sleight 1975<sup>a</sup>, Sleight 1975<sup>b</sup>). This means that after some time they "accept" the new blood pressure and tend to maintain it. This means in turn that the nerve activity is normalized.

#### EFFECT ON TISSUE BLOOD-FLOW OF BLOOD PRESSURE LOWERING TREATMENT

In patients with hypertension and cardiovascular disease the relationship between blood flow and blood pressure can be changed by several means.

Due to structural changes (increased wall-lumen ratio) in the resistance vessels of patients with hypertension the shape of the pressure flow curve is changed so that the lower limit for the autoregulation (as well as the upper limit) is moved to the right (Figure 3). From this follows that the blood flow starts to fall at a higher blood pressure in patients with hypertension than in normotensive individuals. Hypertensive patients faint at a higher blood pressure level than normotensive persons do (Stead & Kunkel 1940).

Arteriosclerotic changes in the big arteries may also influence the flow pressure relationship in these patients. An arteriosclerotic occlusion or obstruction will reduce the local perfusion pressure in the tissue distal to the obstruction in relation to the systemic blood pressure. Therefore the local tissue blood-flow will fall

# ARTERIAL HYPOTENSION AND ITS CONSEQUENCES FOR THE CEREBRAL CIRCULATION

Lennart Hansson

## INTRODUCTION

The blood-flow of the human brain and its relation to arterial pressure has been studied extensively since Wigglesworth developed the inert gas method for determination of cerebral blood-flow (CBF) in 1945 (Kety & Schmidt 1945). The metabolic demands of the brain are comparatively high, resulting in a resting blood-flow of 50-60 ml per minute and 100 g of tissue under resting conditions. This means that approximately 750 ml per minute of arterial blood is needed for the maintenance of cerebral metabolism. This in turn, corresponds to almost 15 % of the resting cardiac output, and due to the high oxygen extraction of the brain means that approximately 20 % of the body's total oxygen consumption goes to this organ (Folkow & Neil 1971).

## AUTOREGULATION OF CEREBRAL BLOOD-FLOW

As in so many other "peripheral" vascular beds, the blood-flow in the cerebral circulation is autoregulated. In other words the CBF is kept constant over a wide range of blood pressure and in this respect the brain is similar to e.g. skeletal muscle, kidney, liver and other organs or organ systems (Johnson 1964, Sjöström 1978).

Findings suggesting autoregulation of blood-flow was first made by Bayliss (1902) who among other things studied the relationship between arterial blood pressure changes and volume changes in the hind limbs of various animals.

Bayliss also found autoregulation of blood-flow in other organs, such as the kidney, and concluded that it is independent of nervous influence (Bayliss 1902).

Several theories have been put forward in order to explain the autoregulation of blood-flow. One of these is the myogenic theory which has been discussed e.g. by Folkow (1964).

In brief this theory depends on the concept that a basal tone exists in the blood vessels. A lowering of blood pressure would then represent a diminished stimulus and therefore lead to vasodilatation which in turn would tend to keep the flow unchanged.

Another theory put forward to explain flow autoregulation is the metabolic theory (Berne 1964). In brief this theory is based on the concept that changes in perfusion pressure will cause metabolic changes in the tissues, e.g. accumulation of metabolites which in turn may induce changes of the vascular calibers so that flow is kept constant.

The third main theory frequently referred to in discussions regarding autoregulation of CBF is the tissue pressure theory. This theory requires that the organ in question is surrounded by very rigid capsule such as the brain within the skull. Elevation of the perfusion pressure will then cause an outward filtration of fluid, which in turn will cause a raised tissue pressure which compresses the vessels to a certain extent thereby keeping flow constant.

The tissue pressure theory would seem to offer a logical explanation of the autoregulation of CBF when arterial pressure is raised. However it is much more difficult to apply this theory in order to explain autoregulation of CBF also when blood pressure is lowered and for this reason the tissue pressure theory would appear to offer a less likely explanation.

It is entirely possible that more than one mechanism of the above mentioned are involved in the autoregulation of CBF. Thus, Lassen has expressed the opinion that both the myogenic theory and the metabolic theory are engaged (Lassen 1959, Lassen 1964). This view has also been expressed by others working in this field, e.g. Harper and Häggendal (1968). Findings supporting the myogenic theory have been reported e.g. by Häggendal and Johansson (1966) and by Ekström-Jodal and co-workers (1969). Further support for the myogenic



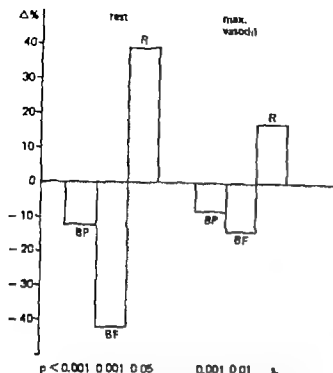


Figure 5 Change in the mean auscultatory blood pressure, calf blood-flow and calf flow resistance at rest and under maximal vasodilatation in a group of patients with mild to moderate blood pressure elevation during 6 weeks of propranolol therapy (320 mg per day range 80-640 mg per day) (n = 16). Vasodilatation was induced by a combination of artery occlusion and calf muscle work until exhaustion.

Reduction of perfusion pressure as regards the blood flow in the extremities is of particular interest

In patients with impaired peripheral circulation, e.g. due to arterial disease as in intermittent claudication. In such a patient reduction of systemic arterial pressure for example caused by antihypertensive therapy may cause an aggravation of ischaemic symptoms such as a further reduction in walking distance. In patients with incipient or manifest gangrene antihypertensive therapy should be avoided if possible with respect to other manifestations of the high blood pressure in the patient. Blood pressure lowering therapy will most likely aggravate the ischaemic symptoms in such patients. In fact treatment with drugs which increase blood pressure, has sometimes been used with good therapeutic results in such patients (Lassen *et al.* 1968).

## CONCLUSIONS

Blood flow in several important peripheral vascular beds is kept constant over a wide range of perfusion pressure (autoregulated). By means of blood pressure reduction below the lower limit of autoregulation, e.g. by antihypertensive therapy and particularly in tissue distal to local obstructions causing further reduction in the perfusion pressure, ischaemic symptoms of varying severity may follow. These symptoms may be severe enough to warrant a withdrawal of blood pressure lowering treatment.

## REFERENCES

- Folkow B: Description of the myogenic hypothesis. *Circ Res* 15: 279-287 1964.
- Folkow B & Neil E. Circulation. Oxford University Press, New York 1971.
- Hansson L. Arterial hypotension and its consequences for the cerebral circulation. *Acta Med Scand suppl* 628: 17-20 1978. (This volume).
- Lassen NA, Larsen OA, Sorensen AWS, Halbäck T, Dahm I, Nilsen R & Westling H. Conservative treatment of gangrene using mineralocorticoid - induced moderate hypertension. *Lancet* i: 606-609 1968.
- Semple SJ & De Wardener HE. Effect of increased renal venous pressure on circulatory autoregulation of isolated dog kidneys. *Circ Res* 7: 643-648 1959.
- Sleight P. Baroreceptor function in hypertension. In: Pathophysiology and management of hypertension. pp 45-53.
- Edic G, Berghand, L, Hansson & L Werko. A Lindgren & Söner. Molndal 1975.
- Sleight P. Neural control of the cardiovascular system. In: Modern trends in cardiology 3. pp 1-43. Ed. M F Oliver. Butterworths, London 1975.
- Stead JA & Kunkel P. Nature of peripheral resistance in arterial hypertension. *J Clin Invest* 19: 25-33 1940.
- Strandgaard S. Autoregulation of cerebral blood flow in hypertensive patients. *Circulation* 53: 720-727 1976.
- Thulesius O. Haemodynamic studies on experimental obstruction of the femoral artery in the cat with special reference to the peripheral action of vasoactive substances. *Acta Physiol Scand* 57 suppl 199: 1-95 1962.
- Thumke K & Kramer K. Weitere Untersuchungen zur myogenen Natur der Autoregulation des Nierenkreislaufes. *Pfluegers Arch* 269: 77-93, 1959.

# ARTERIAL HYPOTENSION AND ITS CONSEQUENCES FOR THE CEREBRAL CIRCULATION

Lennart Hansson

## INTRODUCTION

The blood-flow of the human brain and its relation to arterial pressure has been studied extensively since Harvey developed the inert gas method for determination of cerebral blood-flow (CBF) in 1945 (Kety & Schmidt 1945). The metabolic demands of the brain are comparatively high, resulting in a resting blood-flow of 50-60 ml per minute and 100 g of tissue under resting conditions. This means that approximately 750 ml per minute of arterial blood is needed for the maintenance of cerebral metabolism. This in turn, corresponds to almost 15 % of the resting cardiac output, and due to the high oxygen extraction of the brain means that approximately 20 % of the body's total oxygen consumption goes to this organ (Folkow & Neil 1971).

## AUTOREGULATION OF CEREBRAL BLOOD-FLOW

As in so many other "peripheral" vascular beds, the blood flow in the cerebral circulation is autoregulated. In other words the CBF is kept constant over a wide range of blood pressure and in this respect the brain is similar to e.g. skeletal muscle, kidney liver and other organs or organ systems (Johnston 1964, Sircus 1978).

Findings suggesting autoregulation of blood-flow was first made by Bayliss (1902) who among other things studied the relationship between arterial blood pressure changes and volume changes in the hind limbs of anoxic animals.

Bayliss also found autoregulation of blood-flow in other organs, such as the kidney, and concluded that it was independent of nervous influence (Bayliss 1902).

Several theories have been put forward in order to explain the autoregulation of blood-flow. One of these is the myogenic theory which has been discussed e.g. by Folkow (1964).

In brief this theory depends on the concept that a basal tone exists in the blood vessels. A lowering of blood pressure would then represent a diminished stimulus and therefore lead to vasodilatation which in turn would tend to keep the flow unchanged.

Another theory put forward to explain flow autoregulation is the metabolic theory (Berne 1964). In brief this theory is based on the concept that changes in perfusion pressure will cause metabolic changes in the tissues, e.g. accumulation of metabolites which in turn may induce changes of the vascular calibers so that flow is kept constant.

The third main theory frequently referred to in discussions regarding autoregulation of CBF is the tissue pressure theory. This theory requires that the organ in question is surrounded by very rigid capsule such as the brain within the skull. Elevation of the perfusion pressure will then cause an outward filtration of fluid, which in turn will cause a raised tissue pressure which compresses the vessels to a certain extent thereby keeping flow constant.

The tissue pressure theory would seem to offer a logical explanation of the autoregulation of CBF when arterial pressure is raised. However it is much more difficult to apply this theory in order to explain autoregulation of CBF also when blood pressure is lowered, and for this reason the tissue pressure theory would appear to offer a less likely explanation.

It is entirely possible that more than one mechanism of the above mentioned are involved in the autoregulation of CBF. Thus, Lassen has expressed the opinion that both the myogenic theory and the metabolic theory are engaged (Lassen 1959, Lassen 1964). This view has also been expressed by others working in this field, e.g. Harper and Häggendal (1965). Findings supporting the myogenic theory have been reported, e.g. by Häggendal and Johansson (1966) and by Ekström-Jodal and co-workers (1969). Further support for the myog

enic mechanism is offered by the finding that autoregulation takes place at a lower flow level with a pulsatile flow as compared to non pulsatile flow with the same mean pressure (Held et al 1969). It is interesting to note that the existence of autoregulation of the CBF has been denied by some distinguished researchers even into the 1960's (Sagawa & Guyton 1961). For further extensive discussions on the autoregulation of CBF the reader is referred to references: Lassen 1959, Lassen 1964, Harper 1966 & Ekström-Jodal 1970.

## EFFECTS OF BLOOD PRESSURE CHANGE ON THE CEREBRAL BLOOD-FLOW

As already mentioned CBF is kept constant over a wide range of blood pressure. In fact Lassen suggests that CBF is unchanged at arterial pressures between 60–170 mm Hg (1959). This is supported by studies showing that neither essential hypertension (Moyer et al 1953, Moyer & Morris 1954, Hafkenschiel et al 1954), nor drug-induced hypertension (Moyer et al 1954) was associated with any significant change of CBF. Moreover moderate reduction of blood pressure did not cause a significant change of CBF (Moyer & Morris 1954, McCall 1953).

That autoregulation of CBF cannot be maintained at low arterial pressure has been known for several decades (Lassen 1959). Later studies have demonstrated a breakthrough of autoregulation also at high blood pressures (Strandgaard et al 1973). Of great interest is the fact that the whole autoregulation curve of CBF is shifted to the right in hypertension (Figure 1). This has been demonstrated in hypertensive patients using angiotensin II and the ganglion blocker trimetaphan in order to raise and lower blood pressure respectively (Strandgaard et al 1973). Studies in normotensive baboons and in baboons with two-kidney-Goldblatt hypertension have confirmed this shift of the curve both as regards the upper (Strandgaard et al 1975) and the lower limit of CBF autoregulation (Jones et al 1976). It has been suggested (Strandgaard 1978) that the shift of the autoregulation curve in hypertension to the right is due to structural vascular changes in the precapillary resistance vessels leading to an increased wall to lumen ratio (Folkow et al 1973) (Figure 1).

## CLINICAL IMPLICATIONS

When the lower limit of CBF autoregulation is reached a number of symptoms occur (Table I). Likewise, as blood pressure is increased to above the upper limit of CBF autoregulation increasingly severe symptoms will be seen (Table II). Due to the shifted autoregulation curve hypertensive individuals will tolerate higher blood pressure levels before they experience the symptoms and consequences described in Table II. On the other hand they will also be more susceptible to blood pressure reductions. Particularly when reducing very high blood pressures rapidly symptoms of reduced cerebral perfusion have been reported. Thus, Graham reported two patients with malignant hypertension who both became unconscious after having had their blood pressure reduced from 240/140 mm Hg to 120/85 mm Hg and from 240/170 mm Hg to 120/100 mm Hg respectively by administration of oral bethandine and intravenous pentolinium respectively (Graham 1975). Particularly in elderly hypertensive patients care should be taken not to lower arterial pressure too rapidly (Jones & Graham 1977).

Certain drugs seem to require more care than other. Thus sodium nitroprusside has been shown to increase intracranial pressure (Turner et al 1977). This is probably due to the powerful vasodilating action of this compound which could cause edema of the brain in spite of the reduction in perfusion pressure. In a series of 44 patients undergoing neurosurgery sodium nitroprusside was shown to give an initial increase in intracranial pressure whereas treatment with the

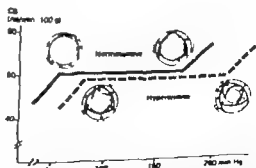


Figure 1 Cerebral blood-flow autoregulation curves in normotension and hypertension. Note shift of curve to the right in hypertension due to structural changes in the precapillary resistance vessels. (Based on Lassen 1959, Ekström-Jodal 1970, Moyer & Morris 1954, Strandgaard et al 1973 and Jones et al 1976)

ganglion blocker trimetaphan did not have this effect (Turner et al 1977). Furthermore, treatment with sodium nitroprusside may give rise to rapid changes in arterial pressure which are too fast for the autoregulation process to be maintained (Fluck 1977). It has also been claimed that CBF autoregulation is lost altogether during treatment with this compound (Crockard et al 1976).

From a practical point of view it therefore appears that special care should be taken when using sodium nitroprusside in situations requiring acute reduction of arterial pressure. During chronic treatment of hypertension particular care is recommended when using peripheral sympatholytic agents, which occasionally may reduce blood pressure drastically e.g. in the standing position or during exposure to heat, with ensuing risks of reduced CBF leading to dizziness or syncope. On the other hand prolonged and gradual reduction of elevated arterial pressure in hypertension will tend to shift the autoregulation curve of CBF back towards normal (Strandgaard to be published). This is probably due to reversibility in the structural vascular changes in the precapillary resistance vessels of the kind described in other vascular beds (Hansson & Svartesson 1975).

## CONCLUSIONS

Cerebral blood-flow is autoregulated over a wide range of arterial pressure. This autoregulation of CBF is shifted towards a higher blood pressure range in hyper-

Table I. Effects of reduced cerebral blood-flow

Discomfort
Dizziness
Sleepiness
Nausea
Syncope
Coma
Death

Table II. Effects of increased cerebral blood-flow

Discomfort
Headaches
Nausea
Mental confusion
Convulsions
Coma
Death (apoplexy)

tensive patients due to structural vascular changes in the precapillary resistance vessels. When reducing blood pressure below the lower limit of autoregulation, potentially dangerous effects may arise such as syncope or unconsciousness. These risks should be born in mind particularly when employing powerful and fast acting antihypertensive agents. On the other hand, prolonged and gradual reduction of arterial pressure through the use of oral antihypertensive agents will tend to shift the autoregulation curve of CBF back towards normal thereby minimizing the risk of cerebral complications due to reduced CBF.

## REFERENCES

- Barnes W M. On the local reactions of the arterial wall to changes of internal pressure. *J Physiol* 28: 220-231 1902.
- Bernie R M. Microbal regulation of blood flow. *Circ Res* 15 suppl 1: 261-268, 1964.
- Crackard H A, Brox F D & Muller J F. Effects of trimetaphan and sodium nitroprusside on cerebral blood flow in rhesus monkeys. *Acta Neurochir* 35: 85-89 1976.
- Ekstrom-Jodal B, Haggendal E, Nilsson N J & Norbäck B. Changes of the transmural pressure. The probable stimulus to cerebral flow autoregulation. In: *Cerebral blood flow*, pp 89-93. Eds M Brock, C Fieschi, D H Ingvar, N A Lassen & K Schummann. Springer Verlag, Berlin, Heidelberg, New York 1969.
- Ekstrom-Jodal B. On the relation between blood pressure and blood flow in the canine brain with particular regard to the mechanism responsible for cerebral blood flow autoregulation. *Acta Physiol Scand* suppl 350 1970.
- Fluck W. Edisional Sodium nitroprusside and the cerebral circulation. *Br J Anaesth* 49: 399-400, 1977.
- Folkow B. Description of the myogenic hypothesis. *Circ Res* 15 suppl 1: 279-287 1964.
- Folkow B & Neil E. *Cerebral Circulation* (a. Circulation, pp 434-448. Oxford University Press, New York, London, Toronto 1971).
- Folkow B, Hallblom M, Lundgren Y, Svartesson R & Werns L. Importance of adaptive changes in vascular design for establishment of primary hypertension, studied in man and in spontaneously hypertensive rats. *Circ Res* 32/33 suppl 1: 2-13 1973.
- Graham D I. Ischaemic brain damage of cerebral perfusion

- failure type after treatment of severe hypertension. *Br Med J* 4: 739, 1975
- Hafkenschiel J H, Friedland C K & Zintel H A. Blood flow and oxygen consumption of the brain in patients with essential hypertension before and after adrenalectomy. *J Clin Invest* 33: 57-62, 1954
- Hansson L & Sivertsson R. Reversibility of structural vascular changes in human essential hypertension. In: Pathophysiology and management of arterial hypertension, pp 114-121. Eder G, Berglund, L, Hansson & L Werkö, A Lindgren & Söner AB Mölndal 1975
- Harper A M. Autoregulation of cerebral blood flow: Influence of the arterial blood pressure on the blood flow through the cerebral cortex. *J Neurol Neurosurg Psychiatry* 29: 398-403, 1966
- Harper A M & Häggendal E. Discussion and comments to section V on autoregulation of CBF. In: Cerebral blood flow and cerebro-spinal fluid III. *Scand J Clin Lab Invest* 22 suppl 102: 102, 1968
- Held J, U. Gottstein U & Niedermayer W. CBF in non-pulsatile perfusion. In: *Cerebral Blood Flow*, pp 94-95. Eds: M Brock, C Fieschi, D H Ingvar, N A Lassen & K Schürmann. Springer Verlag, Berlin, Heidelberg, New York 1969
- Häggendal E & Johansson B. Effects of arterial carbon dioxide tension and oxygen saturation on cerebral blood flow autoregulation in dogs. *Acta Physiol Scand* 66 suppl 258: 27-53, 1966
- Johnson H C. Review of previous studies and current theories of autoregulation. *Circ Res* 15 suppl 1: 2-9, 1964
- Jones J V & Graham D J. Inappropriate antihypertensive therapy in the elderly. *Lancet* i: 425, 1977
- Jones J V, Fitch W, Mackenzie E T, Strandgaard S & Harper A M. Lower limit of cerebral blood flow autoregulation in experimental renovascular hypertension in the baboon. *Circ Res* 39: 455-557, 1976
- Kety S S & Schmidt C F. The determination of cerebral blood flow in man by use of nitrous oxide in low concentrations. *Am J Physiol* 143: 53-66, 1945
- Lassen N A. Cerebral blood flow and oxygen consumption in man. *Physiol Rev* 39: 183-238, 1959
- Lassen N A. Autoregulation of cerebral blood flow. *Circ Res* 15 suppl 1: 1-204, 1964
- McCall M L. Cerebral circulation and metabolism in toxemia of pregnancy. Observations on the effect of Veritrum vend and Apresoline. *Am J Obstet Gynecol* 66: 1015-1030, 1953
- Moyer J H & Morris Jr G C. Cerebral hemodynamics during controlled hypotension induced by a continuous infusion of ganglionic blocking agents. *J Clin Invest* 33: 1001-1003, 1954
- Moyer J H, Morris G & Snyder H. Comparison of the cerebral hemodynamic response to Aramine and norepinephrine in normotensive and hypotensive subject. *Circulation* 10: 265-270, 1954
- Moyer J H, Miller S L, Tashnek A B, Snyder H & Bowman R O. Malignant hypertension and hypertensive encephalopathy: cerebral hemodynamic studies and therapeutic response to continuous infusion of intravenous veratrid. *Am J Med* 14: 175-183, 1953
- Sagawa K & Guyton A C. Pressure flow relationships in isolated canine cerebral circulation. *Am J Physiol* 200: 711-714, 1961
- Sivertsson R. Effect of blood pressure reduction on tissue perfusion. *Acta Med Scand suppl* 628: 13-16, 1978. (This volume)
- Strandgaard S. Academic Dissertation. University of Copenhagen. In press 1978
- Strandgaard S, Olesen J, Skinhøj E & Lassen N A. Autoregulation of brain circulation in severe arterial hypertension. *Br Med J* i: 507-510, 1973
- Strandgaard S, Jones J V, Mackenzie E T & Harper A M. Upper limit of cerebral blood flow autoregulation in experimental renovascular hypertension in the baboon. *Circ Res* 37: 164-167, 1975
- Turner J M, Powell D, Gibson R M & McDowall D G. Intracranial pressure changes in neurosurgical patients during hypotension induced with sodium nitroprusside or trimetaphan. *Br J Anaesth* 49: 419-426, 1977

## DISCUSSION

Ove Anderson

Coronary blood-flow is, of course, subject to autoregulation much as skeletal muscle flow. Although patients may occasionally experience intermittent claudication following reduction of arterial pressure attacks of angina pectoris seem to be rare. Would any body like to comment on this?

Rune Sommerschildt

I believe that this mainly reflects a change in therapeutic policy. Hydralazine in high doses and in conjunction with insufficient  $\beta$ -blockade may cause angina but this is an exception.

Lennart Hansson

Lowering of arterial pressure will favourably influence one of the most important factors in provoking angina, cardiac work. Cardiac oxygen consumption is to a large extent determined by heart rate multiplied by arterial pressure. Agents which decrease heart rate as well as blood pressure will thus tend to diminish the risk of provoking angina.

Sven Hedstrand

In elderly patients further complicating factors may contribute to cause angina pectoris, e.g. AV-block, frequent extrasystolic beats, attacks of tachycardia or postural hypotension, all of which may diminish cerebral blood-flow.

Lennart Hansson

In a majority of hypertensive patients, though, there is a breakthrough of cerebral blood-flow autoregulation

when a sufficiently high blood pressure level is reached.

Olof Forsman

Does vasopressin have any role in the distribution of blood-flow to different tissues, e.g. the brain?

Ramon Snerdsson

I am not aware of studies relating to vasopressin and autoregulation but vasopressin is of interest mainly with regard to blood volume regulation.

Vats Dornheim

Changes in blood viscosity may influence both central and peripheral circulation. Diuretics increase blood viscosity mainly in the initial period of treatment. Do you think that this effect may have clinical consequences?

Lennart Hansson

Blood viscosity is almost invariably determined in vitro but this differs considerably from viscosity in vivo (Dyckowigro et al. 1970). Dogs subjected to step-wise increases in blood loss do not show any significant changes in blood viscosity until the hematocrit value is considerably lowered. However a significant increase of cerebral blood-flow has been demonstrated in patients following reduction of hematocrit by venesection (Thomas et al. 1977). It is not likely though that the small decrease in plasma volume observed during treatment with diuretics will have functionally significant effects on blood viscosity.

## REFERENCES

- Dyckowigro A M, Folchow B, Öberg B & White S W. A comparison of blood viscosity measured *in vitro* and *in vivo*. *Acta Physiol Scand* 78: 70-84, 1970.
- Thomas D J, DuBoulay G H, Marshall J, Pearson T C, Ross Russell R W, Symon L, Wetherley-Mein G & Zilkha E. Effect of haematocrit on cerebral blood-flow in man. *Lancet* 2: 941-943, 1977.

- failure type after treatment of severe hypertension. *Br Med J* 4 739 1975
- Hafkenschiel J H, Friedland C K & Zimel H A. Blood flow and oxygen consumption of the brain in patients with essential hypertension before and after adrenalectomy. *J Clin Invest* 33 57-62, 1954
- Hansson L & Siverstsson R. Reversibility of structural vascular changes in human essential hypertension. In: Pathophysiology and management of arterial hypertension, pp 114-121. Eds: G Berghlund, L Hansson & L Werkö. A Lindgren & Söner AB, Mölndal 1975
- Harper A M. Autoregulation of cerebral blood flow: Influence of the arterial blood pressure on the blood flow through the cerebral cortex. *J Neurol Neurosurg Psychiatry* 29 398-403 1966
- Harper A M & Hägggöndal E. Discussion and comments to section V on autoregulation of CBF. In: Cerebral blood flow and cerebro-spinal fluid III. *Scand J Clin Lab Invest* 22 suppl 102: 102 1968
- Held J, U Goktisch U & Niedermayer W. CBF in non-pulsatile perfusion. In: Cerebral Blood Flow, pp 94-95. Eds: M Brock, C Fieschi, D H Ingvar, N A Lassen & K Schürmann. Springer Verlag, Berlin Heidelberg, New York 1969
- Hägggöndal E & Johansson B. Effects of arterial carbon dioxide tension and oxygen saturation on cerebral blood flow autoregulation in dogs. *Acta Physiol Scand* 66 suppl 258, 27-53 1966
- Johnson P C. Review of previous studies and current theories of autoregulation. *Circ Res* 15 suppl 1 2-9 1964
- Jones J V & Graham D J. Inappropriate antihypertensive therapy in the elderly. *Lancet* i 425 1977
- Jones J V, Fitch W, Mackenzie E T, Strandgaard S & Harper A M. Lower limit of cerebral blood flow autoregulation in experimental renovascular hypertension in the baboon. *Circ Res* 39: 555-557 1976
- Kety S S & Schmidt C F. The determination of cerebral blood flow in man by use of nitrous oxide in low concentrations. *Am J Physiol* 143 53-66 1945
- Lassen N A. Cerebral blood flow and oxygen consumption in man. *Physiol Rev* 39: 183-238 1959
- Lassen N A. Autoregulation of cerebral blood flow. *Circ Res* 15 suppl 1 1 204 1964
- McCall M L. Cerebral circulation and metabolism in toxemia of pregnancy. Observations on the effect of Veratrum viride and Apresoline. *Am J Obstet Gynecol* 66: 1015-1030, 1953.
- Moyer J H & Morris Jr G C. Cerebral hemodynamics during controlled hypotension induced by a continuous infusion of ganglionic blocking agents. *J Clin Invest* 33 1081-1088, 1954
- Moyer J H, Morris G & Snyder H. Comparison of the cerebral hemodynamic response to Aramine and norepinephrine in normotensive and hypotensive subjects. *Circulation* 10: 265-270, 1954
- Moyer J H, Miller S I, Tashnek A B, Snyder H & Bowman R O. Malignant hypertension and hypertensive encephalopathy: cerebral hemodynamic studies and therapeutic response to continuous infusion of intravenous veratrid. *Am J Med* 14 175-183 1953
- Sagawa K & Guyton A C. Pressure-flow relationships in isolated canine cerebral circulation. *Am J Physiol* 200 711-714 1961
- Siverstsson R. Effect of blood pressure reduction on tissue perfusion. *Acta Med Scand suppl* 628, 13-16, 1978 (This volume)
- Strandgaard S. Academic Dissertation. University of Copenhagen. In press 1978
- Strandgaard S, Olesen J, Skinhøj E & Lassen N A. Autoregulation of brain circulation in severe arterial hypertension. *Br Med J* i 937 510 1973.
- Strandgaard S, Jones J V, Mackenzie E T & Harper A M. Upper limit of cerebral blood flow autoregulation in experimental renovascular hypertension in the baboon. *Circ Res* 37 164-167 1975
- Turner J M, Powell D, Gibson R M & McDowall D G. Intracranial pressure changes in neurosurgical patients during hypotension induced with sodium nitroprusside or trimetaphan. *Br J Anaesth* 49 419-426 1977

# ANTIHYPERTENSIVE DRUG REACTIONS FROM DIFFERENT ORGAN SYSTEMS AND FUNCTIONS - AN INTRODUCTION

*Martin Henning*

Adverse drug reactions may appear dose dependent being extensions of the pharmacological actions of the drug. They may also occur with little or no relation to the dosage, mostly constituting allergic reactions. A clinically important aspect is that dose dependent drug reactions are to a large extent predictable and, hence, in many instances preventable. Such reactions make up for 70 to 80 per cent of unwanted drug responses. These facts emphasize the importance of an increased knowledge about side effects of drugs. The well-known truism that no clinically useful drug is devoid of toxicity should be a constant reminder to the clinician and urge to constant attention for the

appearance of probable adverse reactions. Quantification and information are useful means for improving drug safety. It is the purpose of this part of the symposium to discuss in detail the individual tissue or organ untoward responses of antihypertensive drugs which will have to be considered in the all-important risk/benefit relationship of therapy. It has been said that in the ratio adverse effects versus benefit we are uncertain not only of the numerator but also of the denominator. We hope that the presentations of this session will serve to increase the precision of the risk/benefit quotient.





# ADVERSE REACTIONS TO ANTIHYPERTENSIVE DRUGS REPORTED TO THE SWEDISH ADVERSE DRUG REACTION COMMITTEE

Gunnar Boman

A Swedish centre for monitoring of reports on adverse drug reactions (ADRs) as started in 1965 run by a temporary ad hoc committee. In 1971 the activity became permanent and was incorporated into the Department of Drugs, a part of the National Board of Health and Welfare. Since 1975 it is mandatory for all Swedish physicians and dentists to report a) all drug related fatal reactions, b) other serious ADRs and c) new and unexpected ADRs, from both new and old drugs. After the introduction of compulsory reporting about 2,000 reports have been received annually.

All reports are primarily assessed by a medical officer, sometimes after requests for supplementary information. The Adverse Drug Reaction Committee then classifies the causal relationship between the suggested ADR and one or more involved drugs. Relevant details of each report, even those classified as "unlikely" are stored in a computer register and also forwarded to the WHO Collaborating Centre for International Drug Monitoring. In the following all figures relate to reports with a causal relationship classified as "probable or not excluded". It should be noted that the figures for 1977 are preliminary.

## ADVERSE REACTIONS TO ANTIHYPERTENSIVE DRUGS IN GENERAL

For this presentation antihypertensive drugs are defined as drugs included in the following pharmacological groups of the Swedish Register for Pharmaceutical Specialities: Group 2B.12 (beta-receptor blocking agents, "beta-blockers"), 2E (antihypertensive agents) and 2F (diuretics). This means that e.g. beta-blockers used for angina pectoris and diuretics for cardiac insufficiency also will be included. Information on the specific indication is seldom available in the individual reports.

During the last 8 years of operation 10-20 per cent of all reports to the Adverse Drug Reaction Committee

have been related to antihypertensive drugs as defined above (Figure 1). ADRs related to cardiovascular drugs in general constitute the second largest group of reports during the last years. Reports on antibiotic drugs are the most frequent.

## SALES OF CARDIOVASCULAR DRUGS

As a background for the following discussion the sales figures for 1977 regarding beta-blockers and antihypertensive agents are presented in Table I. The sales statistics for diuretics are not included. The sales figures have been calculated as Defined Daily Doses (DDD) and kindly provided by Ingrid Nordenstam, Apoteksbolaget (National Corporation of Pharmacies), Stockholm. The concept of DDD enables a better comparison between the consumption of different drugs than the cost or the number of packages. A preliminary list of DDD for drugs used in Sweden is available from Apoteksbolaget.

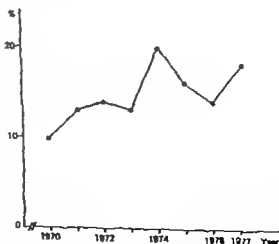


Figure 1. Reports on adverse reactions to antihypertensive drugs as per cent of all reports received by the Swedish Adverse Drug Reaction Committee.



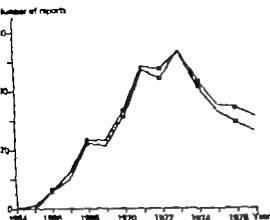


Figure 3 Annual number of reports on adverse reactions to sympatholytic agents (●), thereof to methyldopa (■)

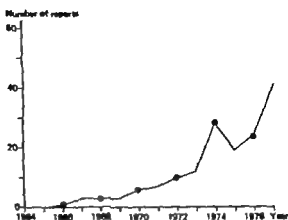


Figure 4 Annual number of reports on adverse reactions to hydralazine

### ADVERSE REACTIONS TO SYMPATHOLYTIC AGENTS

Reports on reactions to sympatholytic agents increased in number up to 1973 (53 reports) but have then declined by each year (Figure 3). This decline probably reflects the diminishing use of this group of drugs. More than 90 per cent of the 389 reactions reported for this group concern adverse effects of methyldopa. The reports on methyldopa during 1965-1975 have recently been analysed (Furhoff 1978).

### ADVERSE REACTIONS TO HYDRALAZINE

Reactions to hydralazine have been reported in increasing numbers during recent years (Figure 4), probably reflecting the increasing use of this drug. In total 157 reports have been received. A peak of 28 reports was observed in 1974 in connection with a study of acetylator status in patients with hydralazine induced lupoid syndrome reported on the Committee (Strandberg et al. 1976).

### REFERENCES

- Furhoff A-K. Adverse reactions with methyldopa - decade reports. *Acta Med Scand*. In press 1978.
- Strandberg I, Boman G, Hamner L & Sjogren F. Acetylator phenotype in patients with hydralazine induced lupoid syndrome. *Acta Med Scand* 200: 367-371 1976.
- Swedish ADR Committee. Report no 22. *Läkertidningen* 72: 2697-2699 1975.

Table 1. Sales of cardiovascular drugs in Sweden 1977  
Source: National Corporation of Pharmacies, Stockholm. 2B = Beta-receptor blocking drugs. 2E = Antihypertensive drugs. DDD = Defined Daily Doses/1,000 inhabitants/day

	DDD	
	2B 12	2E
National average	34	13
County		
Stockholm	24	9
Gothenburg	43	14
Gotland	48	14
Värmland	47	16
Örebro	42	22

Table 1 shows that beta-blocking agents are used twice as much as other antihypertensive agents. Impressive regional differences are also observed 24-48 DDD/1 000 inhabitants/day for the beta blockers and 9-22 for antihypertensive agents. Some examples of regions with obvious deviations from the national average are also shown. A further analysis of the material must be performed before any explanations can be suggested.

#### ADVERSE REACTIONS TO BETA BLOCKERS AND THIAZIDES

The annual numbers of received reports, related to beta-blockers and to thiazides and thiazide like diuretics are shown in Figure 2. In total 365 reports on beta-blockers and 316 reports on these diuretics have been submitted. In the latter group 69 reports on a combination of hydrochlorothiazide and amiloride (Moduretic) are not included. Few adverse reactions to the beta-blockers were reported until 1974 when reports on practolol caused an impressive increase. It is interesting to note that even after the withdrawal of practolol in 1975 the number of reports on beta blockers have remained high. One explanation is the introduction of new beta-blockers during the last years. Another is that the practolol incident made the doctors aware of the fact that this group of drugs really can cause adverse reactions. The reporting pattern for the diuretics is different. After a peak of 36 reports in 1969 the numbers have been constant, i.e. showing a decreasing share in view of the increase in the total reporting in Sweden.

#### ADVERSE REACTIONS TO PRACTOLOL

Practolol (Eraldin<sup>®</sup>) was introduced on the Swedish market in March 1974. During May and June 1974 preliminary reports on serious ocular and cutaneous reactions to practolol were published in the British Medical Journal. Single reports on adverse reactions were received in the following month. In November 1974 the Department of Drugs in view of continued reports in the literature informed all Swedish physicians of these risks and recommended a restriction of the use of practolol. In the following 3 months 20-30 reports on reactions to practolol were received each month. More than 100 reactions were reported before the withdrawal of practolol for oral use in May 1975 (Swedish ADR Committee 1975). It can be noted that no cases of purpura or sclerosing panniculitis related to practolol have been reported in Sweden.

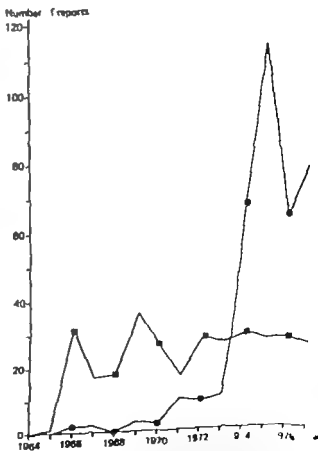


Figure 2. Annual number of reports on adverse reactions to beta-receptor blocking agents (●) and thiazide diuretics (○).

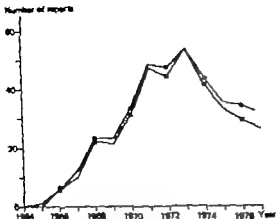


Figure 3 Annual number of reports on adverse reactions to sympatholytic agents (●), thereof to methyldopa (■)



Figure 4 Annual number of reports on adverse reactions to hydralazine

### ADVERSE REACTIONS TO SYMPATHOLYTIC AGENTS

Reports on reactions to sympatholytic agents increased in number up to 1973 (53 reports) but have then declined by each year (Figure 3). This decline probably reflects the diminishing use of this group of drugs. More than 90 per cent of the 389 reactions reported for this group concern adverse effects of methyldopa. The reports on methyldopa during 1965–1975 have recently been analysed (Furhoff 1978).

### ADVERSE REACTIONS TO HYDRALAZINE

Reactions to hydralazine have been reported in increasing numbers during recent years (Figure 4), probably reflecting the increasing use of this drug. In total 157 reports have been received. A peak of 28 reports was observed in 1974 in connection with a study of acetylator status in patients with hydralazine-induced lupoid syndrome reported to the Committee (Strandberg et al 1976).

### REFERENCES

- Furhoff A-K. Adverse reactions with methyldopa—decade reports. *Acta Med Scand* In press 1978.
- Strandberg I, Boman G, Lissner L & Sjöqvist F. Acetylator phenotype in patients with hydralazine induced lupoid syndrome. *Acta Med Scand* 200: 367–371, 1976.
- Swedish ADR Committee Report no 33. *Läkertidningen* 72: 2697–2699, 1975.



# REGISTRATION OF SIDE EFFECTS BY MEANS OF A QUESTIONNAIRE

Ove Andersson

## INTERVIEWER BIAS

It is common knowledge among clinicians in all branches of medicine that details of the patient's symptom picture will often be missed if the patient is not specifically asked whether or not he has had various relevant symptoms. The same situation applies concerning side effects of, for example, anti-hypertensive drugs. This phenomenon is registered objectively through the differences in the incidence of side effects when only spontaneously reported symptoms are recorded and when patients are interviewed according to a standardized check-list. Since there is reason to suspect some degree of under-reporting, owing, among other factors, to the patient's positive attitude towards the therapist, self-administered questionnaires have been introduced for registration of side effects in recent years. The advantages of this approach are obvious: the patient is given an opportunity to report any symptoms at his leisure, without being influenced by the doctor or nurse. The doctor's enthusiasm for a certain mode of therapy can be neglected, especially in comparative trials of double-blind type.

The method also has obvious disadvantages, however: there is a loss of sensitivity as the questionnaire must be kept reasonably short, the patient may have difficulty understanding the questions and finer points may be missed unless supplementary questions are asked. The following questionnaire (Table 1), which has been used for registration of side effects in comparative studies of  $\beta$ -adrenoceptor blocking agents and diuretics, may serve as an example of a self-administered questionnaire.

## INFLUENCE OF THE PATIENT MATERIAL ON THE INCIDENCE OF SIDE EFFECTS

The composition of the patient material with respect to sex, age and organic manifestations of hypertension obviously influences the incidence and nature of re-

ported side effects. There is no other way to explain how the incidence of tiredness as a side effect of methyldopa can vary between 12 and 83% in two different studies (Amery et al. 1970, Pritchard et al. 1968). There are admittedly other differences between these studies, but this example would seem to provide a good illustration of the difficulties in interpreting results from trials in different groups of patients.

Bulpien et al. (1974) have reported clear sex differences in a large trial with overrepresentation of headache, depression of mood and changes of therapy in women compared to men. Although details of treatment effect on blood pressure, age and severity of hypertension are lacking, the material is so large (over 400 patients in each group) that only marked selection in connection with admission of the patients to the study can reduce the general applicability of the findings. Increasing age, which often means an increased frequency of organ damages as well as of co-existing diseases, also leads to an increased incidence of reported side effects such as reduced rate of walking, myxuria, reduced sexual potency and postural hypotension (Bulpien et al. 1974). On the other hand, elderly patients suffered less from headache, depression of mood and somnolence in the same study.

## FREQUENCY OF SYMPTOMS - COMPARISON BETWEEN HYPERTENSIVES AND HEALTHY CONTROLS

When assessing the frequency of symptoms in arterial hypertension reported in self-administered questionnaires it would seem logical to compare healthy subjects with groups of hypertensive patients. A randomized material of healthy and hypertensive 50-year-old men, homogeneous with respect to sex and age, has been studied in Gothenburg (Berghult 1974). A questionnaire comprising 30 questions about the occurrence of symptoms during the preceding three



Table 1 An example of a self-administered questionnaire.

Code:	No = 1	Uncertain = 2	Yes = 3
<i>General question to be asked first</i>			
Do you think that you have had any side effects of the medicine? If yes please state what kind of side effects			<input type="checkbox"/>
I am going to ask you some questions about symptoms that you may have had and I want you to try to remember whether you have had these symptoms or not. (If the patient replies "yes" ask him "Has this been troublesome?")			
Have you been troubled by breathlessness and wheezing in your chest?			<input type="checkbox"/>
Have your ankles become swollen in the evening?			<input type="checkbox"/>
Do you think that your condition in the whole has deteriorated?			<input type="checkbox"/>
Have you had any pain in your chest when going uphill or climbing stairs or at other times when you have exerted yourself?			<input type="checkbox"/>
Have you had any pain in your calf muscles when walking uphill or climbing stairs or when hurrying on even ground?			<input type="checkbox"/>
Do you often have cold hands or feet?			<input type="checkbox"/>
Have you noticed whether your heart beats especially slowly?			<input type="checkbox"/>
Have you noticed whether your heart beats irregularly?			<input type="checkbox"/>
Have you become dizzy or has everything gone black when you get up?			<input type="checkbox"/>
Have you felt dizzy when walking about?			<input type="checkbox"/>
Have you felt nauseated after taking the tablets?			<input type="checkbox"/>
Have you had stomach ache?			<input type="checkbox"/>
Have you had diarrhoea?			<input type="checkbox"/>
Have you been more than usually tired?			<input type="checkbox"/>
Have you felt depressed?			<input type="checkbox"/>
Have you had any difficulties in getting to sleep at night?			<input type="checkbox"/>
Have you often woken up during the night?			<input type="checkbox"/>
Have you had nightmares?			<input type="checkbox"/>

months was used (Lindström & Tibblin 1971). These questions were intended to measure the subject's tendency to report symptoms and concerned both somatic and more unspecific and mental symptoms. The results can be summarized as follows: There were no significant differences in the incidence of symptoms between a reference group, an untreated group and a group of patients receiving antihypertensive therapy. A non-significant tendency towards a higher incidence of many symptoms was recorded in the group of treated hypertensives.

Findings obtained in a study in London (Bulpitt et al 1974) contrast with these results. In age- and sex-matched materials a significantly higher rate of

reporting of symptoms was found among hypertensives with respect to postural hypotension, dryness of the mouth, nycturia, diarrhoea, somnolence, low walking speed, impotence and disturbance of ejaculation. The mean age of the patients and their controls was 55 and 53 years, respectively.

The essential difference between these two studies is that the Gothenburg study concerned general symptoms, whereas the London study comprised specific questions about side effects that commonly occur during the treatment given. The high rate of these subjective side effects is also characteristic in association to treatment with drugs like methyldopa, betanidine, guanethidine and reserpine.

## INCIDENCE OF SYMPTOMS - COMPARISON BETWEEN BEFORE AND AFTER ANTI-HYPERTENSIVE TREATMENT

Whereas comparisons between different groups of patients are difficult, for reasons discussed above, the self-administered questionnaire seems better suited for repeated registration in the same material. The questionnaire must then be adjusted to the therapy prescribed and symptoms should be recorded before and during treatment. The patients may then be divided into four groups:

- a) patients without symptoms,
- b) patients with the same symptoms before and during treatment
- c) patients with new symptoms (side effects?) and
- d) patients whose symptoms disappear

The British are pioneers in this field too. In a follow-up study before and after ten months in 55 normotensive healthy subjects, a spontaneous improvement in most of the previously listed symptoms was recorded (Bulpett et al 1976). The difference between abolished and acquired symptoms tended to be positive. Repeated registration of symptoms before and after treatment of 110 hypertensives showed exactly the same trend.

In our own studies we have used somewhat different approach when evaluating symptoms reported in questionnaires. As a rule, only new symptoms occurring during the treatment have been registered as an expression of side effects. In a comparative study of the hypotensive effect and biochemical and subjective side effects during treatment with hydrochlorothiazide at different dose levels, we found significant reduction in the incidence of reported symptoms with reduction of the dose (Borghard & Andersson 1976). Since the three dose regimes were given in randomized

order the reduction in symptoms cannot have been due to the time factor. In another comparative study (Andersson et al 1976), in which 106 previously untreated patients with mild hypertension were randomly allocated to treatment with bendroflumethiazide (Satures K, 1-2 tablets) or propranolol (Inderal 160 mg once or twice a day), we found no decisive difference during the first twelve months of the study with respect to the effect on the blood pressure or biochemical changes. The incidence of reported symptoms fell significantly during the first two months of treatment with both drugs. A further reduction was observed in both groups during the treatment. Few positive reports being registered.

## SUMMARY

1. Self-administered symptom or side-effect questionnaires may be used to avoid observer bias.
2. Differences in symptom reporting occur between men and women and between different age-groups.
3. The incidence of symptoms declines with time in healthy normotensive controls.
4. With suitable questions, relating to specific side effects, registration of side effects is possible.
5. A causal relationship between side effects and treatment can only be verified by discontinuing the therapy and seeing whether the symptom disappears.
6. Placebo effects can never be excluded.

## CONCLUSIONS

A self-administered questionnaire may be used for follow-up of treatment but should always be supplemented with the therapist's own assessment and evaluation of the connection with the treatment and degree of severity.

## REFERENCES

- Amery A, Verhaeghe M, Borsaeft H & Verstraeten G: Hypotensive action and side effects of cloxacillin-chlorthalidone and methyldopa-chlorthalidone in treatment of hypertension. *Br Med J* 4: 392-395, 1970.
- Andersson O, Borghard G, Larsson O, Werkö L & Wilhelmsson L: Schizofreni eller betablockering vid hypertensionsbehandling. *Ullkarutidningen* 73: 1824-1826, 1974.
- Borghard G: Hypertens och hypotensiva organmanifestationer hos 50-åringar. *Dok. Elanders Boktryckeri Aktiebolag, Kungälv*, 1974.
- Borghard G & Andersson O: Low doses of hydrochlorothiazide in hypertension. Antihypertensive and metabolic effects. *Eur J Clin Pharm* 10: 177-182, 1976.

Bulpitt C J, Dollery C T & Carne S. A symptom questionnaire for hypertensive patients. *J Chron Dis* 27: 309-323 1974

Bulpitt C J, Dollery C T & Carne S. Change in symptoms of hypertensive patients after referral to hospital clinic. *Br Heart J* 38: 121-128 1976

Lindström B & Többlin G. Subjektiva beväis vid angina pectoris och hypertoni. *Hälsö Information* no 14: 1-7 1971

Prichard B N C, Johnston A W, Hill I D & Rosenbaum M L. Bethanidine, guanethidine and methyldopa in treatment of hypertension: a within-patient comparison. *Br Med J* 1: 135-144 1968.

## DISCUSSION

*Bengt Lundh*

Adverse drug reactions are certainly not reported to their true extent and I wonder whether the representatives for the Adverse Drug Reaction Committee have any comments on the difference between the reported and the true incidence of side effects of drugs?

*Gunnar Boman*

Strictly by definition, all hypokalaemias digitalis in-

toxications, insulin induced comas etc. which are associated with hospital care should be reported. This is of course not done and we would like to emphasize the importance of reactions of a somewhat less commonplace character

Also cases of suspected side effects should be reported. Studies of drug induced blood dyscrasias show that one third of all hospitalized patients were reported to the committee.

# ADVERSE REACTIONS TO ANTIHYPERTENSIVE DRUG THERAPY CENTRAL NERVOUS SYSTEM

Matti Hennig

## 1 MENTAL CHANGES

### A Sedation

The term sedative effect is notoriously vague in its definition and is observed with most drugs including placebo. Sedation is also not easily defined in psychological terms and the physiological and pharmacological basis for a sedative action is obscure. Common clinical translations of sedation would appear to be drowsiness, calmness, feeling of lassitude, fatigue or sleepiness during the day. Symptoms such as decrease in ability to concentrate, forgetfulness and prolongation of reaction time are probably other representations of sedation.

As might be expected the patient's experience of this will vary considerably depending on mental set up, activities etc. People engaged in intellectually demanding tasks will naturally suffer more from a sedative effect as will of course those employed in work requiring constant alertness and attention e.g. operating complicated machinery or driving a car.

Table 1 Central nervous side effects of antihypertensive drugs

1	Mental changes	
	A Sedation	clonidine methyldopa reserpine $\beta$ -adrenergic receptor blockers
	B Depression	reserpine methyldopa $\beta$ -adrenergic receptor blockers
2	Sleep disturbances	$\beta$ -adrenergic receptor blockers clonidine reserpine
3	Extrapyramidal symptoms	reserpine methyldopa
4	Neuroendocrinological symptoms	reserpine methyldopa

The introduction of reserpine and other extracts of *Rauwolfia* into antihypertensive treatment and the ensuing outbreak of reserpine-induced depressions made physicians painfully aware of central nervous side effects of antihypertensive agents. It should be noted that unwanted effects of this kind are frequently very difficult to anticipate from animal experiments and depend almost entirely on a careful clinical assessment. So far surprisingly little quantitative information is available on this subject. It appears that a major reason why so little attention has been paid to this aspect in clinical trials is related to the inherent difficulties in separating central nervous symptoms, caused by pharmacological actions of the drugs concerned, from secondary reactions to other side effects, or to other factors, e.g. the effect of being diagnosed as a victim of a life-long disease with treatment according to this.

In attempting to classify central nervous side effects of antihypertensive agents several possibilities arise. The simple process of cataloguing the various drugs and their reported side effects has been avoided. It is clear that drugs interfering with central nervous system (CNS) neurotransmitter metabolism are liable to affect various systems utilizing such transmitters, and a classification might be accordingly based. However in many instances the precise nature of the influence of antihypertensive drugs on central neurotransmitters is not known and therefore a more clinically oriented approach to classification of CNS side effect has been adopted using the type of symptoms as a basis (Table 1). No attempt has been made to cover the full panorama of CNS side effects as found in e.g. Physician's Desk Reference or package inserts. CNS reactions secondary to the lowering of blood pressure are considered elsewhere in this symposium. Hence or possible reference has primarily been made to papers of review character.

Bulpitt C J, Dollery C T & Carne S. A symptom questionnaire for hypertensive patients. *J Chron Dis* 27: 309-323 1974

Bulpitt C J, Dollery C T & Carne S. Change in symptoms of hypertensive patients after referral to hospital clinic. *Br Heart J* 38: 121-128, 1976

Lindström B & Tibblin G. Subjektiva besvär vid angina pectoris och hypertoni. *Hälsö information* no 14: 1-7 1971

Prichard B N C, Johnston A W, Hill I D & Rosenheim M L. Bethanidine, guanethidine and methyldopa in treatment of hypertension: a within-patient comparison. *Br Med J* 1: 135-144 1968.

## DISCUSSION

*Bengt Lindh*

Adverse drug reactions are certainly not reported to their true extent and I wonder whether the representatives for the Adverse Drug Reaction Committee have any comments on the difference between the reported and the true incidence of side effects of drugs?

*Gunnar Boman*

Strictly by definition all hypokalemiæ, digitalis in-

toxications, insulin-induced comas etc. which are associated with hospital care should be reported. This is of course not done and we would like to emphasize the importance of reactions of a somewhat less commonplace character.

Also cases of suspected side effects should be reported. Studies of drug-induced blood dyscrasias show that one third of all hospitalized patients were reported to the committee.

may produce depressional states by a direct action on the CNS. The common denominator seems to be that these agents interfere with the metabolism of CNS neurotransmitters involved in the regulation of mood etc., notably 5-hydroxytryptamine. The best known example of this is the Rauwolfia alkaloids such as reserpine. Several records of reserpine-induced suicidal depression are available (see Goodwin & Bunney 1971; Tester-Dalderup 1975) but the picture includes a full spectrum of symptoms down to quite subtle changes of mood. The incidence of depression during reserpine treatment varies considerably in the literature, many investigations failing to observe significant differences in this respect compared to control groups while other studies indicate figures as high as 25 per cent (Tester-Dalderup 1975). While some of the factors mentioned earlier may contribute to obscure the true incidence it is my personal belief that, using careful diagnostic criteria, the proportion of patients showing reserpine-induced depressive symptoms is really quite high and well motivates the declining usage of this drug in many countries. Apparently the risk increases with large doses but it should be noted that long-term treatment with even small doses affect CNS 5-hydroxytryptamine stores similarly as do large doses for brief periods (Rund & Jurevics 1977).

Methyldopa also depletes CNS monoamine stores although by a mechanism of action different from that of reserpine and affecting chiefly catecholamines, in fact, the anxiolytic effect of methyldopa is largely related to this central effect (Henning 1975). It is not known whether the feeble action of methyldopa on central 5-hydroxytryptamine metabolism explains why this drug is considerably less likely to cause depression than the Rauwolfia alkaloids but it seems quite clear from the literature that frank depression during methyldopa treatment is rare (Tester-Dalderup 1975; Tester-Dalderup 1978). In fact some investigations found no significant association between methyldopa and depression (Dooley & Bulpitt 1975; Smith & McCoubrie 1974) or in one instance not between any of the antihypertensive drugs studied (reserpine, methyldopa and adrenergic blocking agents) and the occurrence of depressive symptoms (Barr 1974). This author concludes that depressions occurring during antihypertensive drug therapy are reflect

ions of the hypertensive disease itself. In spite of this it seems safest to avoid methyldopa in patients with a history of psychiatric disturbance of the depressive type.

The  $\beta$ -adrenergic blocking agents so frequently used in antihypertensive treatment have recently been incriminated in depressional states (Greenblatt et al. 1976; Robinson 1978) but a clear-cut dissociation from peripheral effects of  $\beta$ -adrenergic receptor blockade is hardly possible. In view of the previously mentioned pharmacological prerequisites (Conway et al. 1978) a careful observation of the  $\beta$ -blocker treated patient for the appearance of symptoms of depression would seem indicated. Rare reports of confusional or stuporous states, particularly in elderly people have been associated with  $\beta$ -blocking drugs (Robinson 1978).

Clonidine and its congeners also influence central neurotransmitter metabolism and, like methyldopa, their hypotensive effect depends on an interaction with central catecholamines (Henning 1975). As mentioned sedation is the outstanding central side effect of clonidine and depressional states are but rarely reported, it would appear that most if not all such cases fall within the categories (b) and (c) listed above. The same probably holds true also for the occasional reports of depression associated with other antihypertensive drugs (Barr 1974; Tester-Dalderup 1975; Tester-Dalderup 1978). In one study patients treated with adrenergic neurone blockers of the guanethidine type tended to be more depressed than those on reserpine and methyldopa (Barr 1974) but this is undoubtedly secondary to the severe peripheral side effects of the neurone blockers.

## 2 SLEEP DISTURBANCES

The physiological mechanisms underlying sleep-wakefulness regulation are little known but catecholaminergic pathways from part of the brainstem reticular formation and particularly noradrenaline neurons seem to play a role in such functions (Lidbrink 1974). Drugs interfering with the function of catecholamine neurons are known to affect sleep-wakefulness control: all the agents discussed in the previous section have documented effects on various aspects of this parameter (Greenblatt et al. 1976; Robinson 1978; Tester

The antihypertensive drugs most frequently reputed to affect such activities are nowadays no doubt methyl dopa and clonidine, reserpine being less commonly employed (Tester Dalderup 1975). The pharmacological basis for the sedative effect of these drugs is probably related to their interfering with central adrenergic neuronal systems which are engaged in the regulation of wakefulness and alertness (Lidbrink 1974). The incidence of troublesome sedation in patients taking these drugs is dose-dependent but probably quite high amounting in one careful survey to 51% for methyl dopa (Dollery & Bulpitt 1975). With clonidine it appears to be even more common. Onesti et al (1971) in a series of 90 patients on oral clonidine report sedation in 64%. Recent studies have indicated that the sedative action of methyl dopa may be diminished without losing the antihypertensive effect by giving the drug as a single dose at bedtime (Wright et al 1976). So far no reports are available on the possible influence of this procedure on sleep quality. A decrease in mental acuity, forgetfulness and prolongation of reaction time are other symptoms reported after methyl dopa (Tester Dalderup 1975). A number of experimental agents pharmacologically related to clonidine seem to share the sedative effect with this drug (see e.g. Jäättelä 1976).

Treatment with  $\beta$ -receptor blocking drugs is almost invariably associated with a feeling of tiredness, drowsiness or lassitude. That these agents do exert a sedative action by a direct effect on the CNS is highly probable; the existence of central adrenergic receptors of the  $\beta$ -type is by now fairly well established (see Conway et al 1978) and these drugs are currently being tried in various neuro-psychiatric disorders including anxiety and similar symptoms (Symposium 1976). However, it is not known to what extent the peripheral effects of  $\beta$ -blockade, e.g. lowering of cardiac output and blood pressure and alterations in tissue perfusion may contribute to cause what the patient experiences as a feeling of tiredness etc. Further, the sedative effect of  $\beta$ -blocking drugs is considerably less troubling than for the drugs previously discussed and is usually of little concern compared to other central side effects (vide infra).

Out of other antihypertensive drugs reported to elicit sedative effects, diuretics (Dollery & Bulpitt 1975) and

agents blocking peripheral sympathetic nerve function (e.g. ganglion blocking agents, guanethidine or betanidine) are occasionally mentioned. In these cases, sedation might be secondary to other actions of these drugs, e.g. electrolyte disturbances or orthostatic reactions.

Drug treatment associated with heavy sedation may secondarily lead to disturbances of male sexual functions. This seems to be the case with methyl dopa and clonidine both of which, although not interfering directly with erection or ejaculation (Dollery & Bulpitt 1975) have been reported to cause impotence (Tester Dalderup 1975).

### *B Depression*

As in the case of sedation there are both semantic and diagnostic problems associated with the evaluation of mental depression as a side effect of drug therapy: patients as well as physicians may differ in their criteria when applying the term depression. However, it will usually be expressed as a psychic disturbance of varying severity including one or several of the symptoms of spontaneously occurring endogenous depression, i.e. lowering of mood, anxiety and psychomotor inhibition. A few studies are available (Bart 1974, Sneath & McCoubne 1974) in which special psychiatric rating scales have been employed to quantify the data, however, the majority of investigators use the term depression with little or no diagnostic specification.

When attempting to relate antihypertensive drug therapy to depression it must be taken into account that this may be caused by (a) the antihypertensive agent(s) administered either primarily due to CNS actions or secondarily due to other side effects (e.g. orthostatic reactions, impotence etc.); (b) a secondary reaction to the psychological consequences of being diagnosed as the victim of hypertension; (c) a pure coincidence with spontaneous depression occurring during the treatment. Incidentally this leads to the interesting question whether depressive illness is perhaps more commonly associated with hypertensive disease.

In the individual case it is probably often impossible to systematize in the way outlined above but it seems quite clear that a number of antihypertensive drugs

may produce depressive states by a direct action on the CNS. The common denominator seems to be that these agents interfere with the metabolism of CNS neurotransmitters involved in the regulation of mood etc., notably 5-hydroxytryptamine. The best known example of this is the Rauwolfia alkaloids such as reserpine. Several records of reserpine-induced suicidal depression are available (see Goodwin & Bunney 1971; Tester Daldenup 1975) but the picture includes a full spectrum of symptoms down to quite subtle changes of mood. The incidence of depression during reserpine treatment varies considerably in the literature, many investigators failing to observe significant differences in this respect compared to control groups while other studies indicate figures as high as 25 per cent (Tester Daldenup 1975). While some of the factors mentioned earlier may contribute to obscure the true incidence it is my personal belief that, using careful diagnostic criteria, the proportion of patients showing reserpine-induced depressive symptoms is really quite high and well illustrates the declining usage of this drug in many countries. Apparently the risk increases with large doses but it should be noted that long-term treatment with even small doses affect CNS 5-hydroxytryptamine stores similarly as do large doses for brief periods (Rand & Jurevic 1977).

Methyldopa also depletes CNS monoamine stores although by a mechanism of action different from that of reserpine and affecting chiefly catecholamines, in fact, the antihypertensive effect of methyldopa is largely related to this central effect (Henning 1975). It is not known whether the feeble action of methyldopa on central 5-hydroxytryptamine metabolism explains why this drug is considerably less likely to cause depression than the Rauwolfia alkaloids but it seems quite clear from the literature that frank depression during methyldopa treatment is rare (Tester Daldenup 1975; Tester-Daldenup 1978). In fact, some investigators found no significant association between methyldopa and depression (Dollery & Bulphs 1974; Smith & McCoubrie 1974), or in one instance not between any of the antihypertensive drugs studied (reserpine, methyldopa and adrenergic blocking agents) and the occurrence of depressive symptoms (Bart 1974). This author concludes that depressions occurring during antihypertensive drug therapy are reflex

ions of the hypertensive disease itself. In spite of this it seems safest to avoid methyldopa in patients with a history of psychiatric disturbance of the depressive type.

The  $\beta$ -adrenergic blocking agents so frequently used in antihypertensive treatment have recently been incriminated in depressive states (Greenblatt et al. 1976; Robinson 1978) but a clear-cut dissociation from peripheral effects of  $\beta$ -adrenergic receptor blockade is hardly possible. In view of the previously mentioned pharmacological prerequisites (Cornay et al. 1978) a careful observation of the  $\beta$ -blocker treated patient for the appearance of symptoms of depression would seem indicated. Rare reports of confusional or stuporous states, particularly in elderly people have been associated with  $\beta$ -blocking drugs (Robinson 1978).

Clonidine and its congeners also influence central neurotransmitter metabolism and like methyldopa, their hypotensive effect depends on an interaction with central catecholamines (Henning 1975). As mentioned sedation is the outstanding central side effect of clonidine and depressive states are but rarely reported, it would appear that most if not all such cases fall within the categories (b) and (c) listed above. The same probably holds true also for the occasional reports of depression associated with other antihypertensive drugs (Bart 1974; Tester Daldenup 1975; Tester Daldenup 1978). In one study patients treated with adrenergic neurone blockers of the guanethidine type tended to be more depressed than those on reserpine and methyldopa (Bart 1974) but this is undoubtedly secondary to the severe peripheral side effects of the neurone blockers.

## 2. SLEEP DISTURBANCES

The physiological mechanisms underlying sleep-wakefulness regulation are little known but catecholamine pathways from part of the brainstem reticular formation and particularly noradrenergic neurons seem to play a role in such functions (Lidbrink 1974). Drugs interfering with the function of catecholamine neurons are known to affect sleep-wakefulness control, all the agents discussed in the previous section have documented effects on various aspects of this parameter (Greenblatt et al. 1976; Robinson 1978; Tester



The antihypertensive drugs most frequently reputed to affect such activities are nowadays no doubt methyl dopa and clonidine, reserpine being less commonly employed (Tester Dalderup 1975). The pharmacological basis for the sedative effect of these drugs is probably related to their interfering with central adrenergic neurone systems which are engaged in the regulation of wakefulness and alertness (Lidbrink 1974). The incidence of troublesome sedation in patients taking these drugs is dose-dependent but probably quite high, amounting in one careful survey to 51% for methyl dopa (Dollery & Bulpitt 1975). With clonidine it appears to be even more common, Onesti et al (1971) in a series of 90 patients on oral clonidine report sedation in 64%. Recent studies have indicated that the sedative action of methyl dopa may be diminished without losing the antihypertensive effect by giving the drug as a single dose at bedtime (Wright et al 1976). So far no reports are available on the possible influence of this procedure on sleep quality. A decrease in mental acuity, forgetfulness and prolongation of reaction time are other symptoms reported after methyl dopa (Tester Dalderup 1975). A number of experimental agents pharmacologically related to clonidine seem to share the sedative effect with this drug (see e.g. Jääteila 1976).

Treatment with  $\beta$ -receptor blocking drugs is almost invariably associated with a feeling of tiredness, drowsiness or lassitude. That these agents do exert a sedative action by a direct effect on the CNS is highly probable; the existence of central adrenergic receptors of the  $\beta$ -type is by now fairly well established (see Conway et al 1978) and these drugs are currently being tried in various neuro-psychiatric disorders including anxiety and similar symptoms (Symposium 1976). However it is not known to what extent the peripheral effects of  $\beta$ -blockade, e.g. lowering of cardiac output and blood pressure and alterations in tissue perfusion may contribute to cause what the patient experiences as a feeling of tiredness etc. Further, the sedative effect of  $\beta$ -blocking drugs is considerably less troubling than for the drugs previously discussed and is usually of little concern compared to other central side effects (vide infra).

Out of other antihypertensive drugs reported to elicit sedative effects, diuretics (Dollery & Bulpitt 1975) and

agents blocking peripheral sympathetic nerve function (e.g. ganglion blocking agents, guanethidine or betanidine) are occasionally mentioned. In these cases, sedation might be secondary to other actions of these drugs, e.g. electrolyte disturbances or orthostatic reactions.

Drug treatment associated with heavy sedation may secondarily lead to disturbances of male sexual functions. This seems to be the case with methyl dopa and clonidine both of which, although not interfering directly with erection or ejaculation (Dollery & Bulpitt 1975) have been reported to cause impotence (Tester Dalderup 1975).

### *B Depression*

As in the case of sedation there are both semantic and diagnostic problems associated with the evaluation of mental depression as a side effect of drug therapy: patients as well as physicians may differ in their criteria when applying the term depression. However it will usually be expressed as a psychic disturbance of varying severity including one or several of the symptoms of spontaneously occurring endogenous depression, i.e. lowering of mood, anxiety and psychomotor inhibition. A few studies are available (Bart 1974, Smith & McCoubrie 1974) in which special psychiatric rating scales have been employed to quantify the data, however the majority of investigators use the term depression with little or no diagnostic specification.

When attempting to relate antihypertensive drug therapy to depression it must be taken into account that this may be caused by (a) the antihypertensive agent(s) administered either primarily due to CNS actions or secondarily due to other side effects (e.g. orthostatic reactions, impotence etc.); (b) a secondary reaction to the psychological consequences of being diagnosed as the victim of hypertension; (c) a pure coincidence with spontaneous depression occurring during the treatment. Incidentally this leads to the interesting question whether depressive illness is perhaps more commonly associated with hypertensive disease.

In the individual case it is probably often impossible to systematize in the way outlined above but it seems quite clear that a number of antihypertensive drugs

may produce depressional states by a direct action on the CNS. The common denominator seems to be that these agents interfere with the metabolism of CNS neurotransmitters involved in the regulation of mood etc., notably 5-hydroxytryptamine. The best known example of this is the Rauwolfia alkaloids such as reserpine. Several records of reserpine-induced suicidal depression are available (see Goodwin & Bunney 1971; Tester-Dalderup 1975) but the picture includes a full spectrum of symptoms down to quite subtle changes of mood. The incidence of depression during reserpine treatment varies considerably in the literature: many investigators failing to observe significant differences in this respect compared to control groups while other studies indicate figures as high as 25 per cent (Tester-Dalderup 1975). While some of the factors mentioned earlier may contribute to obscure the true incidence, it is my personal belief that, using careful diagnostic criteria, the proportion of patients showing reserpine-induced depressive symptoms is really quite high and will motivate the declining usage of this drug in many countries. Apparently the risk increases with large doses but it should be noted that long-term treatment with even small doses affect CNS 5-hydroxytryptamine stores similarly as do large doses for brief periods (Rand & Jurevics 1977).

Methyldopa also depletes CNS monoamine stores although by a mechanism of action different from that of reserpine and affecting chiefly catecholamines, in fact the antihypertensive effect of methyldopa is largely related to this central effect (Hemming 1975). It is not known whether the feeble action of methyldopa on central 5-hydroxytryptamine metabolism explains why this drug is considerably less likely to cause depression than the Rauwolfia alkaloids but it seems quite clear from the literature that frank depression during methyldopa treatment is rare (Tester-Dalderup 1975; Tester-Dalderup 1978). In fact, some investigators found no significant association between methyldopa and depression (Dollery & Bulpett 1975; Smith & McCoubrie 1974), or in one instance not between any of the antihypertensive drugs studied (reserpine, methyldopa and adrenergic blocking agents) and the occurrence of depressive symptoms (Bart 1974). This author concludes that depressions occurring during antihypertensive drug therapy are reflex

ions of the hypertensive disease itself. In spite of this it seems safest to avoid methyldopa in patients with a history of psychiatric disturbance of the depressive type.

The  $\beta$ -adrenergic blocking agents so frequently used in antihypertensive treatment have recently been incriminated in depressional states (Greenblatt et al. 1976; Robinson 1978) but a clear-cut dissociation from peripheral effects of  $\beta$ -adrenergic receptor blockade is hardly possible. In view of the previously mentioned pharmacological prerequisites (Conway et al. 1978) a careful observation of the  $\beta$ -blocker treated patient for the appearance of symptoms of depression would seem indicated. Rare reports of confusional or stuporous states, particularly in elderly people have been associated with  $\beta$ -blocking drugs (Robinson 1978).

Clonidine and its congeners also influence central neurotransmitter metabolism and like methyldopa, their hypotensive effect depends on an interaction with central catecholamines (Hemming 1975). As mentioned, sedation is the outstanding central side effect of clonidine and depressional states are but rarely reported; it would appear that most if not all such cases fall within the categories (b) and (c) listed above. The same probably holds true also for the occasional reports of depression associated with other antihypertensive drugs (Bart 1974; Tester-Dalderup 1975; Tester-Dalderup 1978). In one study patients treated with adrenergic neurone blockers of the guanethidine type tended to be more depressed than those on reserpine and methyldopa (Bart 1974) but this is undoubtedly secondary to the severe peripheral side effects of the neurone blockers.

## 2 SLEEP DISTURBANCES

The physiological mechanisms underlying sleep-wakefulness regulation are little known but catecholaminergic pathways from part of the brainstem reticular formation and particularly noradrenergic neurones seem to play a role in such functions (Lindbrink 1974). Drugs interfering with the function of catecholaminergic neurones are known to affect sleep-wakefulness control: all the agents discussed in the previous section have documented effects on various aspects of this parameter (Greenblatt et al. 1976; Robinson 1978; Tester

Dalderup 1975 Tester Dalderup 1978). The table lists  $\beta$ -blockers, clonidine and reserpine but it is difficult to establish whether any clearcut difference exists between the three drugs. The  $\beta$ -blocking agents through their common use will be recognized as most commonly causing disturbances of sleep ranging from insomnia to vivid sometimes hallucinatory dreams, somnambulism and violent behaviour with ensuing amnesia. These sometimes alarming but rarely serious central side effects of  $\beta$ -blocking agents can be prevented or minimized by administering the major part or the full daily dose of the drug early in the day, avoiding dosage at night. It has been claimed that certain  $\beta$ -blocking agents are less prone to this type of side effect and this has been related to a poor penetration through the blood brain barrier (Robinson 1978). Although these agents certainly differ in their avidity to pass this barrier it is doubtful whether such differences are of significance in the clinical situation involving long term treatment in which some kind of an equilibrium is probably established. Carefully controlled studies allowing a settlement of this issue are not available but certainly called for.

Clonidine has been reported to cause insomnia and vivid dreams (Tester Dalderup 1975) but the incidence of this side effect is probably lower than after  $\beta$ -blockers. Reserpine treatment may lead to an increase in the duration of paradoxical (REM) sleep and to nightmares (Tester Dalderup 1975). Methyldopa appears to affect sleep to a less extent than the previously mentioned drugs; there was a slight prolongation of the time slept in one study (Dollery & Bulpitt 1975) but no mention is made of the quality of the sleep. Tester Dalderup (1975) lists occasional disturbing nightmares during methyldopa therapy.

### 3 EXTRAPYRAMIDAL SYMPTOMS

Extrapyramidal side effects of antihypertensive drugs are almost exclusively encountered in patients receiving reserpine who may display symptoms of the parkinsonian type ranging in severity from relatively mild rigidity and dyskinesia to a full-blown Parkinson's syndrome, indistinguishable from the spontaneously occurring variety (Goodwin & Bunney 1971, Tester Dalderup 1975). These cases are usually seen after large doses of reserpine and their pharmacological back-

ground is an interference of reserpine with brain dopamine metabolism (Rand & Jurevics 1977). Extrapyramidal symptoms have also been reported during methyldopa treatment but the incidence is considerably lower than after reserpine (Sweet et al. 1972). Methyldopa has actually been tried in conjunction with levodopa in parkinsonian patients (Sweet et al. 1972) but in view of the ambiguous results it is recommended that methyldopa should be avoided in patients with extrapyramidal disturbances.

### 4 NEUROENDOCRINOLOGICAL DISTURBANCES

Neuroendocrine effects are caused by drugs interfering with the catecholamine neurone systems controlling the release of the hypothalamic hypophyseotropic hormones or "factors" (Buckingham 1977). Among drugs used in the therapy of hypertension these central side effects are confined to reserpine and its analogues and methyldopa. Both drugs, by impairing dopamine neurotransmission in the hypothalamus cause an increase in the release of prolactin. hyperprolactinemia is apparently quite common during treatment with these drugs but it is comparatively rare that this leads to symptoms such as gynaecomastia or galactorrhea (Tester Dalderup 1975). The highly controversial issue of reserpine treatment possibly being associated with mammary cancer is aptly reviewed by Tester Dalderup (1978). Clonidine which in clinical doses does not appreciably interfere with dopamine neurotransmission has not been reported to influence neuroendocrine functions.

### CONCLUSIONS

Most antihypertensive drugs cause central nervous system side effects but it is difficult to single out primary central nervous actions from those secondary to other side reactions. This is particularly evident in the case of mental symptoms such as sedation or depression. However antihypertensive agents which interfere with CNS neurotransmitter functions are clearly able to elicit primary CNS side effects. Although many of these adverse reactions may appear quite alarming to the patient, they are, with the notable exception of depressive states, rarely of a serious nature *quo ad vitam*. However by their subjective unpleasant

antihypertensive agents. Therefore, this field would profit from closer attention in future clinical trials of both old and new drugs, particular focus being placed on quantitation of data.

## REFERENCES

- Bent W. Do antihypertensive drugs really cause depression? *Proc R Soc Med* 68: 919-921, 1974.
- Buckingham J. The endocrine function of the hypothalamus. *J Pharm Pharmacol* 29: 649-656, 1977.
- Cherry J, Greenwood DT & MacLennan DM. Central nervous actions of  $\beta$ -adrenoceptor antagonists. *Clin Sci Mol Med* 44: 119-124, 1973.
- Dollery CT & Roberts CJ. Alphenethyldopa. In: Central actions of drugs in blood pressure regulation, pp 256-266. Eds: DS Davies & JL Reid. Pitman Medical Publishing Co Ltd, Tunbridge Wells, Kent, 1975.
- Goodwin FK & Beerley WE. Depressions following reserpine: A reevaluation. *Section Psychiatry J* 433-448, 1971.
- Greenblatt DJ, Shader RI & Koch-Weser J. The psychopharmacology of beta adrenergic blockade: pharmacological and epidemiological aspects. *Adv Clin Pharmacol* 12: 6-12, 1976.
- Hemmig M. Central sympathetic transmitters and hypertension. *Clin Sci Mol Med* 48: 195-203, 1975.
- Rizala A. Comparison of BS 100-141 and clonidine as antihypertensive agents. *Eur J Clin Pharmacol* 10: 73-76, 1976.
- Lubinski P. The effect of lesions of ascending noradrenergic pathways on sleep and waking in the rat. *Brain Res* 74: 79-80, 1974.
- Oniciu G, Buck K D, Helmuth V, Kun K E & Morgan P. Clonidine: A new antihypertensive agent. *Am J Cardiol* 28: 74-83, 1971.
- Proceedings of a Symposium: Neuro-psychiatric effects of adrenergic beta-receptor blocking agents. *Adv Clin Pharmacol* 12, 1976.
- Ward NJ & Jurevics H. The pharmacology of Rauwolfia alkaloids. *Mit E. p Pharmacol* 39: 77, 1977.
- Robinson BF. Anti-anginal and beta adrenoceptor blocking drugs. Side effects of drugs annual 2: 166-179, 1978.
- Smith RP & McComb M. Antihypertensive drugs and depression. *Psychol Med* 4: 393-398, 1974.
- Sweet RD, Lee JE & McDowell FI. Methyl dopa as an adjunct to levodopa treatment of Parkinson's disease. *Clin Pharmacol Ther* 13: 23-27, 1972.
- Tesser-Dalderup CBM. Hypertensive drugs. Side effects of drugs 8: 461-482, 1975.
- Tesser-Dalderup CBM. Hypertensive drugs. Side effects of drugs annual 2: 187-199, 1978.
- Wright J M, McLeod P J & McCullough W. Antihypertensive efficacy of single bedtime dose of methyl dopa. *Clin Pharmacol Ther* 20: 733-737, 1976.



# VASOSPASTIC PHENOMENA IN PATIENTS TREATED WITH BETA ADRENOCEPTOR BLOCKING AGENTS

Kerth Olsson, Lars-Erik Linn and Kersin Sundkvist

## INTRODUCTION

Raynaud's phenomenon usually consists of episodic attacks of decreased finger circulation characterized by white fingers and paresthesias, followed by a cyanotic phase and a hyperemic phase with reddening of the skin. In some patients the cyanotic phase is absent. Half of the male patients only exhibit pallor. In about 40 per cent of all patients concomitant affliction of hands and feet is seen (Himes & Christensen 1945). When a Raynaud's phenomenon exists in the absence of conditions to which it may be secondary it is called Raynaud's disease or primary Raynaud's phenomenon. It is predominantly found among younger women (see *ratio* 4:1). The classical description of Raynaud's phenomenon includes induction of symptoms by cold, but some studies have failed to show an abnormal decrease in hand blood-flow after local cooling (Downey & Frewin 1973). Others have given evidence of a diminished finger blood-flow (Coffman & Cohen 1971). The pathogenesis of primary Raynaud's phenomenon or Raynaud's disease is still controversial. Although a sympathetic hyperactivity has been implied as a causative factor, no hypersensitivity for norepinephrine or increased plasma contents of the substance has been proven (Coffman & Davies 1975). A decreased resting hand blood-flow but normal vasodilatation after sympathetic release by warming, suggests an excessive sympathetic activity and rules against structural arterial disease (Pearlock 1959). At least in mild cases, normal finger arteries are seen on biopsy (Coffman & Davies 1975).

During recent years, a secondary form of Raynaud's phenomenon or vasospasm has been described as a complication to treatment with beta-adrenergic receptor blocking drugs (Frohlich et al. 1969). Beta blocking drugs have worsened claudication intermittens in patients with a previously known peripheral arterial insufficiency but have also provoked symptoms in per-

sons devoid of earlier signs of ischaemic vascular disease (Rodger et al. 1976). The figures given for the incidence of these side effects vary to a great extent between different authors. This may reflect differences in the actual interest taken in this particular side effect and less serious vasospastic phenomena seem to be quite frequent. Zacharias (1976) made a thorough study of 390 patients treated for 6 months with propranolol. He found slightly troublesome peripheral coldness in 73 per cent of the patients who also received a diuretic. No reduction of the doses were necessary in these patients. Cases of severe Raynaud's phenomenon necessitating complete withdrawal of the drug or reduction of the dose, appeared in a frequency of only 3 per cent. This figure is in good agreement with what others have found (Table I). In contrast Marshall et al. (1976) found a very high incidence of vasospasm complicating different forms of beta-blocking therapy as compared to treatment with methyldopa 4% and 5 per cent respectively. Beta-blocking drugs without intrinsic activity was considered to give this side effect more frequently than those with intrinsic activity or a higher degree of cardioselectivity. Vasospastic phenomena has, however, been described with different types of beta-receptor-blocking agents including cardioselective drugs. Preexisting vasospasm is thus a relative contraindication for this kind of treatment (Weil-Manning 1976). The aim of the present paper was to study the peripheral circulation in patients with va-

Table I Incidence of vasospastic phenomena in patients treated with propranolol

Authors		Incidence %
Frithard & Gilman	(1969)	3
Tarazi & Dunstan	(1972)	4
Comery	(1975)	3
Greenblatt & Koch-Weser	(1976)	6
Dalgaard et al.	(1976)	0.5



### Temperature measurements

The patients were studied in a sitting position at a room temperature of 23–24°C. Both hands were immersed in cold water (19°C, 15 min). The skin temperature of the pulps of the first and third finger and the skin fold between the first and second finger were measured before cooling, immediately after 5, 10 and 15 minutes after the end of cooling. The increase in skin temperature ( $\Delta^{\circ}\text{C}$ ) was calculated from the difference between the temperature registered 15 minutes after and immediately after the end of the cooling. The finger with the lowest skin temperature immediately after the end of the cooling was used for the measurements. When the measurements after cooling were finished the patient was placed in a supine position and vasodilated with 30–40 ml 50 per cent peroral alcohol and an abdominal heating box (40°C, 40 min). The skin temperature was measured as described above during the warming at 10, 20, 30 and 40 minutes.

### Fluorescent angiography

Fluorescent angiography was performed with rapid sequence recording technique (Lund 1976).

### Arterial blood pressure

Arterial blood pressure was measured in both arms with blood pressure cuff on the upper arm. The diastolic blood pressure was registered in Korotkoff phase 5. Mean arterial pressure was calculated as diastolic pressure plus one third of the pulse pressure.

### Digital plethysmographic recordings

Digital plethysmographic recordings with strain gauge technique were made from the third finger of both

hands for registration of the finger pulse curve and blood pressure.

### Forearm blood-flow

Forearm blood-flow (ml/100 ml/min) at rest was measured by venous occlusion plethysmography with an air-filled plethysmograph placed around the forearm according to Dohn (1956) and Graf & Westerstam (1959). The circulation of the hand was occluded by a cuff inflated to 150 mm Hg. The collection cuff placed around the upper arm was inflated to 50 mm Hg.

Statistical analyses were performed with Student's *t*-test including paired observations.

## RESULTS

In all patients, disregarding treatment with selective or non-selective beta-blocker, the digital plethysmography and peripheral arterial blood pressure were normal. All patients reached a temperature of 30°C or more after 40 minutes of indirect heating suggesting a normal ability for vasodilatation. The forearm blood flow during treatment with both selective and non-selective beta-blockers was normal compared to controls (Tables III and IV).

### Cardiovascular beta blockade therapy (3 patients)

In all patients but one, treated with metoprolol, the skin temperature reaction after cooling was pathological, i.e. the skin temperature registered 5 minutes after the end of cooling was below 30°C. The skin temperature before cooling, the increase after cooling ( $\Delta^{\circ}\text{C}$ ), and the forearm blood-flow were not significantly changed when verbutaline was added (Table III). Fluorescent angiography was performed in four

Table III. Skin temperature, skin temperature reaction, heart rate, mean arterial pressure, diastolic blood pressure and forearm blood-flow in eight patients during treatment with metoprolol and after addition of verbutaline.

	Metoprolol	Metoprolol + verbutaline	
Skin temperature before cooling ( $^{\circ}\text{C}$ )	27.2 $\pm$ 3.0	27.4 $\pm$ 3.9	n.s.
Increase in skin temperature after cooling ( $\Delta^{\circ}\text{C}$ )	3.9 $\pm$ 5.1	5.1 $\pm$ 4.3	n.s.
Heart rate (beats/min)	52 $\pm$ 10	58 $\pm$ 7	$p < 0.05$
Mean arterial pressure (mm Hg)	95 $\pm$ 11	100 $\pm$ 11	$p < 0.01$
Diastolic blood pressure (mm Hg)	82 $\pm$ 9	85 $\pm$ 10	$p < 0.05$
Forearm blood-flow (ml/100 ml/min)	3.8 $\pm$ 0.8	3.7 $\pm$ 1.2	n

Reference values 3.8  $\pm$  1.3 ml/100 ml/min (Ekdand et al 1974)



sospastic phenomena before and after the addition of a beta 2 stimulant, terbutaline, and to discuss the possible mechanisms causing vasospasm during treatment with beta-receptor-blocking agents.

## PATIENTS

Twenty-one patients, one female and twenty males, age  $53 \pm 6$  years (mean  $\pm$  SD), developed vasospastic phenomena during treatment with beta-receptor blocking drugs. Eight patients had a previous history of myocardial infarction, thirteen were hypertensives. Diagnoses, WHO classification and therapy are listed in Table II. No clinical signs or previous histories of collagenous disease were registered. All patients had a normal sedimentation rate and plasma electrophoresis. They had no anemia, leucopenia, antinuclear factors or cryoglobulins. Fasting blood glucose was normal and no patient had glucosuria. Thirteen patients were smokers. Thirteen patients were treated with a cardioselective drug and eight with a non-selective one. Half of the patients also received other drugs but this treatment was held constant during the study (Table II).

On an average the vasospastic symptoms appeared after two months of treatment. The most common complaints were cold and white fingers with decreased sensibility. One third of the patients reported symptoms even when staying indoors. Peripheral cyanosis and paresthesias were found in six patients. In many cases intense active rewarming of the hands was required for relief of the symptoms. Four patients had a previous history of cold hands, one also suffered from migraine. Seven patients experienced cold feet, but none had claudication intermittens.

## METHODS

The patients were examined before and 3 weeks after adding terbutaline to the beta-blocker therapy which was held constant during the study. All investigations were performed in the morning. The patients had taken their regular morning dose of medicine before arriving at the laboratory. They were requested not to drink coffee or tea or smoke for 4 hours before the test.

Table II. Diagnoses, WHO classification and therapy in twenty-one patients with vasospasm during treatment with beta-blocking drugs

Patient no	Diagnosis	WHO group	Beta-blocking therapy	Daily dose mg	Other drugs
1	Primary hypertension	I	metoprolol	200	hydrochlorothiazide
2	Primary hypertension	I	metoprolol	200	-
3	Primary hypertension	I	metoprolol	200	hydralazine, hydrochlorothiazide
4	Primary hypertension	II	metoprolol	200	-
5	Hypertension, chronic glomerulonephritis	II	metoprolol	200	-
6	Primary hypertension	I	metoprolol	400	hydrochlorothiazide
7	Primary hypertension	I	metoprolol	400	-
8	Primary hypertension	I	metoprolol	400	hydrochlorothiazide
9	Primary hypertension	I	propranolol	80	bendroflumethiazide, dipyridamol
10	Hypertension, chronic glomerulonephritis	I	propranolol	240	hydrochlorothiazide
11	Primary hypertension	I	timolol	10	-
12	Primary hypertension	I	timolol	20	-
13	Primary hypertension	III	timolol	20	hydrochlorothiazide, hydrochlorothiazide
14	Myocardial infarction		metoprolol	100	-
15	Myocardial infarction		metoprolol	100	furosemide, hydrochlorothiazide
16	Myocardial infarction		metoprolol	100	digoxin
17	Myocardial infarction		metoprolol	150	furosemide
18	Myocardial infarction		metoprolol	150	digoxin
19	Myocardial infarction		alprenolol	150	furosemide
20	Myocardial infarction		alprenolol	400	-
21	Myocardial infarction		alprenolol	400	digoxin

### Temperature measurements

The patients were studied in a sitting position at a room temperature of 23–24°C. Both hands were immersed in cold water (15°C, 15 min). The skin temperature of the pulps of the first and third finger and the skin fold between the first and second finger were measured before cooling, immediately after 5, 10 and 15 minutes after the end of cooling. The increase in skin temperature ( $\Delta^{\circ}\text{C}$ ) was calculated from the difference between the temperature registered 15 minutes after and immediately after the end of the cooling. The finger with the lowest skin temperature immediately after the end of the cooling was used for the measurements. When the measurements after cooling were finished the patient was placed in a supine position and vasodilated with 30–40 ml 80 per cent per oral alcohol and an abdominal heating box (40°C, 40 min). The skin temperature was measured as described above during the warming at 10, 20, 30 and 40 minutes.

### Fluorescent angiography

Fluorescent angiography was performed with rapid sequence recording technique (Lund 1976).

### Arterial blood pressure

Arterial blood pressure was measured in both arms with a blood pressure cuff on the upper arm. The diastolic blood pressure was registered in Korotkoff phase 5. Mean arterial pressure was calculated as diastolic pressure plus one third of the pulse pressure.

### Digital plethysmographic recordings

Digital plethysmographic recordings with strain gauge technique were made from the third finger of both

hands for registration of the finger pulse curve and blood pressure.

### Forearm blood flow

Forearm blood flow (ml/100 ml/min) at rest was measured by venous occlusion plethysmography with an air-filled plethysmograph placed around the forearm according to Dohn (1956) and Graf & Westerstam (1959). The circulation of the hand was occluded by a cuff inflated to 150 mm Hg. The collection cuff placed around the upper arm was inflated to 50 mm Hg.

Statistical analyses were performed with Student's *t* test including paired observations.

## RESULTS

In all patients, disregarding treatment with selective or non-selective beta-blocker the digital plethysmography and peripheral arterial blood pressure were normal. All patients reached a temperature of 30°C or more after 40 minutes of indirect heating suggesting a normal ability for vasodilatation. The forearm blood flow during treatment with both selective and non-selective beta-blockers was normal compared to controls (Tables III and IV).

### Cardioselective beta-blocking therapy (8 patients)

In all patients but one, treated with metoprolol the skin temperature reaction after cooling was pathological, i.e. the skin temperature registered 5 minutes after the end of cooling was below 30°C. The skin temperature before cooling, the increase after cooling ( $\Delta^{\circ}\text{C}$ ), and the forearm blood-flow were not significantly changed when terbutaline was added (Table III). Fluorescent angiography was performed in four

Table III Skin temperature, skin temperature reaction, heart rate, mean arterial pressure, diastolic blood pressure and forearm blood-flow in eight patients during treatment with metoprolol and after addition of terbutaline

	Metoprolol	Metoprolol + terbutaline	
Skin temperature before cooling ( $^{\circ}\text{C}$ )	27.2 $\pm$ 3.0	27.4 $\pm$ 3.9	n.s.
Increase in skin temperature after cooling ( $\Delta^{\circ}\text{C}$ )	3.9 $\pm$ 5.1	5.1 $\pm$ 4.3	n.s.
Heart rate (beats/min)	52 $\pm$ 10	58 $\pm$ 7	$p < 0.05$
Mean arterial pressure (mm Hg)	95 $\pm$ 11	100 $\pm$ 11	$p < 0.01$
Diastolic blood pressure (mm Hg)	82 $\pm$ 9	85 $\pm$ 10	$p < 0.05$
Forearm blood flow (ml/100 ml/min)	2.8 $\pm$ 0.8	3.7 $\pm$ 1.2	n.s.

Reference values 3.8  $\pm$  1.3 ml/100 ml/min (Eidson et al 1974)

Table IV. Skin temperature, skin temperature reaction, heart rate, mean arterial pressure, diastolic blood pressure, forearm blood-flow in six patients during treatment with a non-selective beta-blocker and after addition of terbutaline

	Non-selective beta-blocker	Non-selective beta-blocker + terbutaline	
Skin temperature before cooling (°C)	26.8 ± 4.2	29.4 ± 4.4	n.s.
Increase in skin temperature after cooling (Δ°C)	9.4 ± 4.5	5.9 ± 4.6	n.s.
Heart rate (beats/min)	58 ± 10	56 ± 11	n.s.
Mean arterial pressure (mm Hg)	107 ± 12	103 ± 6	n.s.
Diastolic blood pressure (mm Hg)	93 ± 13	91 ± 7	n.s.
Forearm blood-flow* (ml/100 ml/min)	3.2 ± 1.3	3.2 ± 1.5	n.s.

Reference values 3.8 ± 1.3 ml/100 ml/min (Ekdund et al. 1974)

of the patients during treatment with metoprolol and after addition of terbutaline. The appearance time decreased from 24 ± 6 seconds (mean ± SD) to 20 ± 4 seconds. Reference values 12–15 seconds (Pernow – to be published). No statistical analyses were made.

#### *Non-selective beta blocking therapy (5 patients)*

In all patients treated with a non-selective drug, the skin temperature reaction after cooling was pathological i.e. the skin temperature registered 5 minutes after the end of cooling was below 30°C. The skin temperature before cooling, the increase after cooling (Δ°C) and the forearm blood flow was not significantly changed when terbutaline was added (Table IV). The heart rate, the mean arterial pressure and the diastolic blood pressure was also unchanged after the addition of terbutaline (Table IV).

### DISCUSSION

Our patients have shown symptoms of vasospasm ranging from increased preexisting peripheral coldness to development of classical Raynaud's phenomena. In some cases severe vasospasm has occurred even without provocation by cold. There seems to be no relation between the degree of blood pressure reduction and the occurrence of symptoms. Several facts support our view that the vasospastic complaints were caused by the beta-blocker therapy. As stated above primary Raynaud's disease shows a female predominance. In our material the reverse was true. The incidence of smoking was comparable to the population in general. Other forms of secondary Raynaud's phenomena were excluded with reasonable certainty. In

some patients a reduction of the dose gave some relief of the symptoms and whenever medication was withdrawn the vasospastic phenomena were abolished or brought back to the preexisting level.

Beta-blocking agents decrease cardiac output and may thereby deteriorate the peripheral circulation particularly in patients with a previously diminished blood flow of the extremities. Julius et al. (1972) have conveyed the hypothesis that the reduction of the blood volume after intravenously administered propranolol would depend on a blockade of a tonic dilatation of small blood vessels mediated by beta adrenergic receptors. A diminished circulating blood volume would then cause impairment of the peripheral circulation. Established hypertension is characterized by a normal cardiac output but an elevated total peripheral resistance. After acute administration of propranolol cardiac output is decreased but blood pressure is maintained because of an elevation of vascular resistance. After long-term treatment cardiac output is still decreased but to a smaller extent and the peripheral resistance readjusts towards the initial value (Hansson et al. 1974). After chronic antihypertensive therapy a partial normalization of peripheral resistance after maximal vasodilatation has been found indicating reversibility of structural abnormalities (Sverrisson & Hansson 1976). In our own patients finger pulse curves, blood pressures and ability of vasodilatation were all normal indicating the absence of organic lesions. The forearm blood flow was normal in all patients during beta-blocker therapy. This suggests that the flow decrease was localized to the skin and subcutaneous tissue of the peripheral parts of the limbs.

and may imply that a decreased cardiac output did not contribute to any significant extent to the peripheral vasospasm.

Another plausible explanation for Raynaud's phenomena in patients on beta-blockers is a primary effect on the receptors in the peripheral vascular system. The receptor theory by Lands et al. (1967) has been modified after the finding that differential blockade pattern were produced in the cat heart using different receptor agonists and antagonists (Carlsson et al. 1972). This finding has later been confirmed in human aorta (Abiad et al. 1974) and guinea pig bronchi (Furchgott & Wajsbide 1975). Carlsson et al. (1972) suggested that these findings are best explained by the hypotheses that both beta-1 and beta-2 receptors coexist in the same tissue and mediate the same response. The proportions between these receptors might vary from tissue to tissue and also between individuals from the same species. The highly cardioselective drugs has induced severe bronchospasm in some patients. According to Wahl-Manning & Simpson (1971), this could be explained by assuming that beta-1 receptors are of great importance for mediating relaxation of bronchial smooth muscle in these very patients.

As stated above some evidence exists for different types of beta-receptors mediating vasodilatation in different tissues. This, in turn, might explain the occurrence of peripheral vasospasm among patients treated with a cardioselective beta-blocker assuming the existence of predominantly beta-1 receptors in their skin vessels. In recent thesis, Belkridge (1978) showed the existence of beta-1 receptors in subcutaneous vessels mediating vasodilatation. It is not known if derangements of the subcutaneous circulation can cause Raynaud's phenomena. Different therapeutic measures for Raynaud's phenomena have mainly consisted of attempts to influence the sympathetic nervous system. Good results have been reported after local sympathectomy (Grifford et al. 1958) and after treatment with alpha-receptor-blocking substances (Taylor et al. 1965). Nassa (1973) described a patient with bronchial asthma who was cured from a Raynaud's phenomenon by treatment with terbutaline, a highly selective beta-2 receptor agonist. When given as a single drug it produces a compensatory tachycardia and an increase in cardiac output (Arner et al. 1970). The pe-

ripheral resistance is substantially decreased (Sackner et al. 1975). Both primary and secondary Raynaud's phenomena have been successfully treated with terbutaline (Zabel et al. 1974) but the effect has tended to be of short duration (Thune & Fyhrand 1976).

In combination with propranolol in spontaneously hypertensive rats, terbutaline had no effect on blood pressure whereas the combination with metoprolol resulted in a significant blood pressure reduction (Mallat et al. 1977). The probable interpretation of this finding is that only metoprolol could allow peripheral vasodilatation mediated by beta-2 receptor stimulation. Andersson & Berglund (1975) could not confirm an additive blood pressure effect in patients after adding salbutamol to previous propranolol treatment. In our patients, a significant increase in calculated mean arterial pressure when adding terbutaline to the treatment with a cardioselective drug was found. In patients treated with non-selective drugs the mean arterial pressure was unchanged. This is taken as evidence for a remaining ability to dilate peripheral vessels and increase cardiac output in patients on cardioselective drugs. The increase in calculated mean arterial pressure still remains unexplained. The forearm blood flow however showed no significant increase after the addition of terbutaline. An increase in heart rate was found in patients treated with metoprolol. The absence of tachycardia during active warming suggests a blockade of cardiac beta-receptors, but does not seem to exclude the possibility of a reflex increase in heart rate following vasodilatation after terbutaline.

After the addition of terbutaline the temperature reaction to local cooling did not show any significant improvement. In a few patients, however the appearance time of fluorescein decreased suggesting increased skin blood-flow. It is too early to state whether this could be due to methodological factors only or to a reflection of a true non-responsiveness to the beta-stimulant. The hypotheses of a different receptor population in patients with vasospasm cannot yet be examined because we still lack definite data from our prospective study and from provocation tests.

Another explanation for the somewhat paradoxical reaction of vasospasm on selective beta-blockers might be an increased sensitivity to blockade in the beta-2

receptors of these patients. Metoprolol has a fifty fold increased affinity for beta 1 receptors compared to beta 2 receptors (Åblad et al 1973) but assuming a different sensitivity one might encounter a different response. A deficient beta 2 receptor might be blocked even by the weak action of a cardioselective agent and the ensuing alpha-adrenergic dominance could then cause the vasospasm. A number of studies have given evidence for different peripheral actions of cardioselective and non-selective beta blockers. Åblad et al (1973) studied haemodynamic effects in conscious dogs and found that propranolol and metoprolol had the same lowering effect on cardiac output and no blood pressure reducing action because of a reflex vasoconstriction. However during epinephrine infusion only propranolol gave rise to an increase in blood pressure because of beta 2 receptor blockade. Johnsson (1975) made similar findings in human volunteers. This difference in peripheral action between different types of beta blockers was confirmed after long term oral treatment at rest (van Herwaarden et al 1977) and acutely during isometric exercise (Sangvik et al 1976). In patients who had developed vasospastic side effects during treatment with non-selective drugs Marshall et al (1976) found improvement after changing to a drug with a higher degree of intrinsic activity and Waal Manning (1976) recommends changing the therapy from non selective to cardioselective drugs in angina patients with symptoms of peripheral coldness. Hansson et al (1976) studied side effects during long term treatment with atenolol. In 94 patients with this drug only one case of Raynaud's phenomenon and 4 cases of cold extremities were found.

In conclusion, many different theories could be delivered to explain why vasospastic phenomena occur during treatment with beta-adrenergic-receptor blocking drugs. Several studies indicate that an alpha-adrenergic sympathetic dominance can give disturbances in the peripheral haemodynamics, probably by the elimination of the ability of beta-2 mediated vasodilatation. It is, however still unknown if this could affect the skin circulation and temperature regulation. Vasospastic phenomena arise after treatment with both non-selective and cardioselective drugs. Quantitative differences might exist, but this question, like that of the origin of the phenomenon remains to be definitely answered. Clinically it would be advisable to prescribe beta-blocking drug cautiously in patients with preexisting signs of peripheral vascular disease.

## SUMMARY

Twenty-one patients developed Raynaud's phenomenon during treatment with beta-adrenoceptor blocking agents. The vasospastic symptoms were obviously related to the treatment, but their pathogenesis is still controversial. A decrease in cardiac output might explain the phenomenon. According to our very preliminary data an alpha-adrenergic dominance caused by a direct effect on the peripheral circulation seems more probable. Vasospastic symptoms may arise after treatment with both cardioselective and non-selective beta blocking agents. Cautious prescription of beta blocking drugs to patients with preexisting peripheral vascular disease is recommended.

## REFERENCES

- Andersson O & Berghult O: Antihypertensive effect of beta-1-receptor blockade and beta-2 receptor stimulation in essential hypertension. *Acta Med Scand* 197; 495-496, 1975.
- Amer B, Bertier A, Karlefors T & Westling H: Circulatory effects of oxiprenaline, adrenaline and a new sympathomimetic beta-receptor-stimulating agent, terbutaline, in normal human subjects. *Acta Med Scand suppl* 512: 25-32, 1970.
- Belfrage E: Studies on the control of blood flow and lipolysis by alpha- and beta-adrenoceptors in canine subcutaneous adipose tissue. Thesis Stockholm. In press 1978.
- Carlsson E, Åblad B, Brändström A & Carlsson H: Differential blockade of the chronotropic effects of various adrenergic stimuli in the cat heart. *Life Sci* 11: 953-958, 1972.
- Coffman JD & Cohen AS: Total and capillary fingertip blood flow in Raynaud's phenomenon. *N Engl J Med* 285: 259-263, 1971.
- Coffman JD & Davies W T: Vasospastic diseases: review. *Prog Cardiovasc Dis* 18: 123-146, 1975.
- Conway J: Beta adrenergic blockade and hypertension. In

- Modern trends in cardiology pp 376-403. Ed M F Oliver Vol 3 Butterworths, London 1975
- Dalgaard T, Hjemson L, Iversen A, Jaderberg E, Lindborg B, Lindahl T, Olsson W, Treis F & Wahlberg P. Long-term follow-up of 207 hypertensive outpatients treated with propranolol. *Läkertidningen* 73: 3736-3758, 1976.
- Dohn K. Plethysmographic studies during functional states recording volume changes in ml per 100 ml of extremity. *Rep Skand Hosp* 6: 147-168, 1956
- Downey JA & Frewin DB. The effect of cold on blood flow in the hand of patients with Raynaud's phenomenon. *Clin Sci* 44: 279-289, 1973.
- Eklund B, Kalfjer L & Knutsson E. Blood flow in resting (control) arm and leg during vascular contraction. *J Physiol* 240: 111-124, 1974
- Frohlich ED, Tarazi RC & Dustan HP. Peripheral arterial insufficiency: A comparison of beta-adrenergic blocking therapy. *JAMA* 208: 2471-2472, 1969
- Partridge RF & Waldeck TD. Evidence for both beta-1 and beta-2 receptors in guinea pig tracheal smooth muscle and variation of the beta-1/beta-2 ratio in different animals. Abstract no 150L, p 622. South East Congr Pharmacol Helsinki, Finland 1975
- Gifford JR, W Hemes JE & Craig WM. Sympathocutaneous for Raynaud's phenomenon. *Circulation* 17: 5-13, 1958
- Olef K & Wessman A. Untersuchungen über Regenerations- und Verwendungsphänomene eines fluoreszierenden Exozytosephosphors. *Acta Physiol Scand* 46: 1-18, 1959
- Greenblatt DJ & Koch-Weser J. Adverse reactions to beta-adrenergic receptor blocking drugs: a report from the Boston collaborative drug surveillance program. *Drugs* 7: 118-129, 1974
- Hansson L, Zwieler A J, Jakes S & Hestor S N. Hemodynamic effects of acute and prolonged beta-adrenergic blockade in essential hypertension. *Acta Med Scand* 196: 27-34, 1974
- Karlsson L, Karlberg BE, Åberg H, Westerlund A, Jansson S & Henningsen NC. Long-term hypotensive effect of atenolol (ACD6 012) - new beta-adrenergic blocking agent. *Acta Med Scand* 199: 257-261, 1976
- van Herwaarden C L A, Benkhof R A, Fennis J F M & van't Laar A. Effects of adrenaline during treatment with propranolol and metoprolol. *Br Med J* 1: 1029, 1977
- Holmes EA & Christensen NA. Raynaud's disease among men. *JAMA* 129: 1-4, 1945
- Johnson G. Influence of metoprolol and propranolol on hemodynamic effects induced by adrenaline and physical work. *Acta Pharmacol Toxicol* 36 suppl 5: 59-68, 1975
- John S, Pascual AV, Abrecht PH & London R. Effects of beta-adrenergic blockade on plasma volume in human subjects. *Proc Soc Exp Biol Med* 140: 985-986, 1972
- Lund A M, Arnold A, McAuliff J P, Ludgren F P & Brown J T G. Differentiation of receptor systems activated by sympathomimetic amines. *Nature* 214: 597, 1967
- Lund F. Fluorescein angiography especially of the upper extremities. *Acta Chir Scand suppl* 465: 60-70, 1976.
- Maloney J, Gantley E, Lundgren B, Carlsson E & Fellenius E. Acute hypotensive effect of combined beta-1-adrenoceptor blockade and beta-2-adrenoceptor stimulation in spontaneously hypertensive rats (SHR). *Eur J Pharmacol* 41: 13-16, 1977
- Marshall AJ, Roberts C J C & Barlett D W. Raynaud's phenomenon as a side effect of beta-blockers in hypertension. *Br Med J* 1: 1498-1499, 1976.
- Naes K. Beta-blokkere og beta-stimulering og Raynaud's syndrom. *Tidsskr Nor Lægeforen* 93: 1255-1256, 1973.
- Peacock J H. A comparative study of the digital cutaneous temperatures and hand blood flows in the normal hand, primary Raynaud's disease and primary acrocyanosis. *Clin Sci* 18: 25-33, 1959
- Pernow B. *Perifer cirkulation. Kliniska fysiologiska under sömnstörrelser*. Almqvist & Wiksell Förlag AB, Stockholm in Press 1978
- Prichard B N C & Gellum P M S. Treatment of hypertension with propranolol. *Br Med J* 1: 7-16, 1969
- Rodger J C, Sheldon CD, Lenz RA & Livingston WR. Intravenous blockade complicating beta-blockade. *Br Med J* 1: 1125, 1976.
- Sackner MA, Dougherty R, Watson II & Wessner A. Hemodynamic effects of epinephrine and terbutaline in normal man. *Chest* 68: 616-624, 1975
- Sangvik K, Solbakk M, Lundeth-Dalén E M & Nyberg G. Circulation reaction at rest and during isometric and dynamic exercise in hypertensive patients: influence of different adrenergic beta-adrenoceptor antagonists. *Pharmacotherapeutica* 1: 71-83, 1976
- Servatius R & Hasselwood L. Effects of blood pressure reduction on the structural vascular abnormality in tibia and muscle vascular beds in human essential hypertension. *Clin Sci Med* 51: 77-79, 1976
- Tarazi RC & Dustan HP. Beta-adrenergic blockade in hypertension: Practical and theoretical implications of long-term hemodynamic variations. *Ann J Cardiol* 29: 633-640, 1972
- Taylor SH, Sutherland GR, MacKenzie G J, Staunton HP & Donald KW. The circulatory effect of phenolamine in man with particular respect to changes in forearm blood flow. *Clin Sci* 28: 265-284, 1965
- Thomsen P & Frydend O. Further observations on the therapy with a beta-stimulating agent in Raynaud's phenomenon. *Acta Chir Scand suppl* 465: 84-86, 1976
- Wahl-Manning H J. Experience with beta-adrenoceptor blockers in hypertension. *Drugs* 11 suppl 1: 164-171, 1976.
- Wahl-Manning H J & Simpson F W. Proctol treatment in asthma. *Lancet* 2: 2261, 1970
- Zabel J, Frydend O & Thomsen P. Plethysmographical and clinical observations on Bricetyl therapy in Raynaud's phenomenon. *Acta Derm Venereol (Stockh)* 54: 391-395, 1974

Zacharias F J. Patient acceptability of propranolol and occurrence of side effects. *Postgrad Med J* 52 suppl 4: 87-89, 1976

Åblad B, Carlsson E & Ek L. Pharmacological studies of two new cardioselective adrenergic beta-receptor antagonists. *Life Sci* 12: 107-119, 1973

Åblad B, Carlsson B, Carlsson E, Dahlöf C, Ek L & Håkberg E. Cardiac effects of beta-adrenergic receptor antagonists. *Adv Cardiol* 12: 290-302, 1974

# KIDNEY DAMAGE INDUCED BY ANTIHYPERTENSIVE TREATMENT

Nels C. Hewingson

The frequency of patients with severe essential hypertension who demonstrate progressive impairment of kidney function during treatment is high. The main reason for that is an imperfect control of the blood pressure. Side-effects from the pharmacological treatment play only a limited role. It is now generally accepted that even patients with renal hypertension with or without renal insufficiency only get benefits of pharmacologically induced normotension (Wahlson 1953, Pettigrew 1976, Bengtsson et al. 1968). The kidney damage may be severe (creatinine  $> 400 \mu\text{mol/l}$ ) and the glomerular filtration rate decreasing despite normotension, but the cardiovascular system is more or less protected demonstrated by a lower frequency of vascular catastrophes (Veterans Administration 196-1970).

The above mentioned sentences does not mean that negative effects on renal function during antihypertensive treatment do not exist, but the problem has, however a limited clinical impact. During the last ten years only eight reports of overtaken side-effects

from the kidneys have been reported to the Swedish Board for Drugs side-effects (Table I) and some of these are probably not related to the suspected drug.

This report is only dealing with published or own experience of negative effects on kidney function and only drugs who are used today are discussed.

## PATIENTS WITH NORMAL RENAL FUNCTION

More than 80% of all hypertensive patients can be referred to this group

### Thiazides

Treatment with thiazides for hypertension is widespread all over the world and some reports of kidney damage have occurred (Lyons et al. 1973, Muehrcke & McWilliam 1963, Kjellbo et al. 1965, Dodds & Foord 1970, Fitzgerald 1960). Some of these have been quite specific as the few reported cases of renal necrotizing vasculitis (Kjellbo et al. 1965) or idiopathic interstitial nephritis (Lyons et al. 1973) which in most cases have

Table I. All overtaken side-effects from the urogenital system during antihypertensive treatment recorded at the Swedish Board for Drug side-effects

Drug and dosage	Symptoms	Drug related
Inderal (propranolol)	20 MG 4 oliguria	++
Inderal (propranolol)		+++
Inderal (propranolol)	40 MG x 2 polyuria hematuria + hemospermia	+
Dichloride (hydrochlorothiazide)	50 MG 1 proteinuria	+
Hyproton (chlorazotone) + Aproton (hydralazin)	50 MG x 1 + urinary III MG 3 retention	+
Modemor (acetaldehyde) + Lasec (furosemide)	5 MG 1 increase of 40 MG 1 creatinine (200-400 $\mu\text{mol/l}$ ) nausea	++
Fendrin-K (hydrochlorothiazide)	25 MG x 1 hematuria	
Modemor (hydrochlorothiazide, acetaldehyde)	50 MG x 1 increase of 5 MG x 1 creatinine	+++



Zacharias F J. Patient acceptability of propranolol and occurrence of side effects. *Postgrad Med J* 52 suppl 4: 87-89, 1976

Åblad B, Carlsson E & Ek L. Pharmacological studies of two new cardioselective adrenergic beta-receptor antagonists. *Life Sci* 12: 107-119, 1973

Åblad B, Carlsson B, Carlsson E, Dahl M C, Ek L & Hultberg E. Cardiac effects of beta-adrenergic receptor antagonists. *Adv Cardiol* 12: 290-302, 1974

ing agents: atenolol, pindolol, propranolol and metoprolol. After a run-in period the patients were given the drugs in random order each period lasting for four weeks. The serum TG concentration was increased significantly during treatment with all these beta-adrenoceptor blocking drugs and the percent increase of the serum TG concentration varied between 25% and 63%. The serum cholesterol concentration remained unchanged.

### THE OSLO STUDY

In a study of hypertensive patients the basic treatment was 50 mg hydrochlorothiazide per day. If the blood pressure was not normalized 0.5–1.5 g of  $\alpha$ -methyl dopa was added. If the patients had intolerable side effects during this treatment therapy was shifted and instead 80–320 mg propranolol per day was given. Patients on hydrochlorothiazide +  $\alpha$ -methyl dopa did not exhibit any significant changes of the serum lipid concentrations. However patients on hydrochlorothiazide + propranolol had a mean serum TG concentration elevation from 1.87 to 2.45 mmol/l ( $p < 0.01$ ). The serum cholesterol concentration remained unchanged.

### THE GOTHENBURG STUDY

In the Gothenburg study Berglund (1978) treated men for 4 years with either bendroflumethiazide (Satures-K) or propranolol (Inderal). Whole serum cholesterol was significantly reduced during treatment with both these drugs whereas men on propranolol demonstrated a significant increase of the TG fraction from 1.8 to 2.3 mmol/l (28%  $p \leq 0.001$ ). The data do not permit an analysis in what lipoprotein fraction the cholesterol reduction took part. However since VLDL TG increased it is most likely that the reduction of cholesterol might have occurred in the HDL fraction, which is inversely correlated to the VLDL concentration.

### MECHANISMS OF LIPOPROTEIN METABOLISM DISTURBANCE

Several studies have thus indicated that beta-adrenoceptor blocking agents and diuretics may cause considerable changes in the serum lipid and lipoprotein pattern. A summary of these studies is shown in the Table I. What are the possible mechanisms leading to these changes?

The beta-adrenoceptor blocking effect on lipolysis

Table I. Serum lipid changes after treatment with antihypertensive drugs. Statistically significant differences are shown in % and significance is indicated as \*  $p < 0.05$ , \*\*  $p < 0.01$  and \*\*\*  $p < 0.001$  (ns = no significance).

Author	Treatment duration	Antihypertensive therapy	TG	Cholesterol
Ames & Hill (1976)	3 months	diet + chlorthalidone	+26% ***	+5% **
Berglund (1978)	4 years	Bendroflumethiazide	+13% *	-9% ***
		Propranolol	+28% ***	-7% ***
Wiel Manning (1976)	1 year	Metoprolol	+37% **	ns
Nilsson (1977)	3 months	Metoprolol	ns	ns
Shaw (1978)	1 month	Atenolol	+62%	ns
		Pindolol	+28%	ns
		Propranolol	+37%	ns
		Metoprolol	+25%	ns
Helgeland (1978)	3 years	Hydrochlorothiazide + methyl dopa	ns	ns
		Hydrochlorothiazide + propranolol	+31% **	ns
Tanaka (1976)	2 months	Propranolol	ns	ns
			(VLDL TG +49% ** apo-HDL	-20% **)

and FFA release in the acute situation does not eliminate the possibility that an overshoot occurs when the effect of the drug has diminished or disappeared. The study of Tazaka et al (1976) in fact demonstrates that increased FFA concentrations may be observed after long-term treatment with propranolol.

Another hypothetical explanation for the increase of the TG concentration is an impaired elimination of TG in peripheral tissues. Barboriak and co-workers (1977) demonstrated that after two weeks treatment with propranolol the clearing time after a fatty meal had increased significantly.

## LIPOPROTEIN DIFFERENCES

Almost all of the studies referred to have only dealt with whole serum lipid analyses. What do these changes correspond to in terms of lipoprotein concentrations?

An increase of total serum TG concentration with unchanged or even lowered total cholesterol concentration is most likely the result of the following metabolic development (Figure 1): The increase of total serum TG concentrations is generally a reflection of an increase of the VLDL TG concentration, since the TG concentration in the LDL and HDL lipoprotein fractions are of minor importance from a quantitative point of view and vary little. When the VLDL TG concentration increases, the cholesterol concentration will also increase in proportion, since the TG/cholesterol ratio in this fraction is fairly constant under these circumstances. Furthermore, there is a negative relationship between the VLDL concentration and the HDL concentration, well established from several previous studies. As consequence of the VLDL increase the HDL concentration is lowered (Carlson 1978).

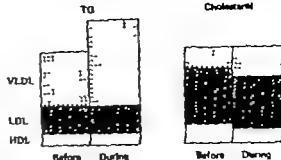


Figure 1. Hypothetic: Serum lipoprotein changes after treatment with diuretics or beta-adrenoceptor blocking agents.

The fact that total cholesterol remains unchanged in many of the studies cited above can thus be explained by the combination of an increase of VLDL cholesterol and a concomitant reduction of similar magnitude of HDL cholesterol. As a result of these changes the patient has now developed a hypertriglyceridaemia with lowered HDL concentrations. Both an increase of the VLDL TG concentration and the lowered HDL concentration are factors which carry increased risks for development of atherosclerotic manifestations. Thus the metabolic alteration induced by the antihypertensive treatment could have unfavourable effects on serum lipoprotein concentrations and composition. Shaw et al. (1978) conclude their paper with the following comment: "If plasma triglyceride levels remain elevated during long term treatment of hypertension with beta-adrenoceptor antagonists, do the benefits outweigh the risks?"

In Table I the reviewed studies are compiled.

It seems obvious from this review that there is a great need for long-term studies of the effects of antihypertensive treatment on lipoprotein metabolism in patients with elevated blood pressure. In order to achieve this, lipoprotein analysis are indispensable.

## REFERENCES

- Ames R P & Hill P. Increase in serum lipids during treatment of hypertension with chlorothalidone. *Lancet* 1 721-723, 1976.
- Barboriak J J & Friedberg H D. Propranolol and hypertriglyceridaemia. *Atherosclerosis* 17 31-35, 1973.
- Berglund G. Fyra års uppföljning av blodtrycksnedsättning och metabol förändringar under färdens-K och Linderalbehandling. *Översikt i Medicin Förening* 3 39-42, 1978.
- Carlson L P. Pernicious nonhypercholesterolemia. *Lipidology* 11 211-213, 1978.
- Helgeland A, Hjemmen I, Holme I & Leren P. Serum triglycerides and serum uric acid in untreated and thiazid-treated patients with mild to moderate hypertension. *Am J Med Sci* 34-38, 1978.
- Newman H J. Comparison of the antilipolytic effect of metoprolol, acebutolol, and propranolol in man. *Br Med J* 2 601-603, 1977.

ing agents: atenolol, pindolol, propranolol and metoprolol. After a run-in period the patients were given the drugs in random order, each period lasting for four weeks. The serum TG concentration was increased significantly during treatment with all these beta-adrenoceptor blocking drugs, and the percent increase of the serum TG concentration varied between 25% and 63%. The serum cholesterol concentration remained unchanged.

### THE OSLO STUDY

In a study of hypertensive patients the basic treatment was 50 mg hydrochlorothiazide per day. If the blood pressure was not normalized, 0.5–1.5 g of  $\alpha$ -methyl dopa was added. If the patients had intolerable side effects during this treatment, therapy was shifted and instead 80–320 mg propranolol per day was given. Patients were treated for a period of 3 years. Patients on hydrochlorothiazide +  $\alpha$ -methyl dopa did not exhibit any significant changes of the serum lipid concentrations. However, patients on hydrochlorothiazide + propranolol had a mean serum TG concentration elevation from 1.87 to 2.45 mmol/l ( $p < 0.01$ ). The serum cholesterol concentration remained unchanged.

### THE GOTHENBURG STUDY

In the Gothenburg study Berglund (1978) treated men for 4 years with either bendroflumethiazide (Salures-k) or propranolol (Inderal<sup>®</sup>). Whole serum cholesterol was significantly reduced during treatment with both these drugs, whereas men on propranolol demonstrated a significant increase of the TG fraction from 1.8 to 2.3 mmol/l (28%  $p \leq 0.001$ ). The data do not permit an analysis in what lipoprotein fraction the cholesterol reduction took part. However, since VLDL TG increased it is most likely that the reduction of cholesterol might have occurred in the HDL fraction, which is inversely correlated to the VLDL concentration.

### MECHANISMS OF LIPOPROTEIN METABOLISM DISTURBANCE

Several studies have thus indicated that beta-adrenoceptor blocking agents and diuretics may cause considerable changes in the serum lipid and lipoprotein pattern. A summary of these studies is shown in the Table 1. What are the possible mechanisms leading to these changes?

The beta-adrenoceptor blocking effect on lipolysis

Table 1. Serum lipid changes after treatment with antihypertensive drugs. Statistically significant differences are shown in % and significance is indicated as:  $p < 0.05$ ,  $p < 0.01$  and  $*** p < 0.001$  (ns = no significance).

Author	Treatment duration	Antihypertensive therapy	TG	Cholesterol
Ames & Hill (1976)	3 months	diaz + chlorothalidone	+26%***	+5%**
Berglund (1978)	4 years	Bendroflumethiazide	+13% <sup>ns</sup>	-9%***
		Propranolol	+28%***	-7%***
Wael-Manning (1976)	1 year	Metoprolol	+37%**	ns
Nilsen (1977)	3 months	Metoprolol	ns	ns
Stew (1978)	2 months	Atenolol	+62%	ns
		Pindolol	+28%	ns
		Propranolol	+37%	ns
		Metoprolol	+25%	ns
Helgeland (1978)	3 years	Hydrochlorothiazide + methyl dopa	ns	
		Hydrochlorothiazide + propranolol	+31%**	ns
Tanaka (1976)	2 months	Propranolol	ns	ns
			(VLDL-TG +49%** apo-HDL)	-20%**

# NEGATIVE CONSEQUENCES OF REDUCTION OF BLOOD PRESSURE - INFLUENCE ON SEXUAL FUNCTION

Rune Sannerstedt

Although it has long been known that treatment with antihypertensive drugs may have an adverse effect on sexual function, and these side effects have been a common phenomenon ever since the days of the ganglion blockers, the otherwise so voluminous hypertension literature contains little information on this point. This is perhaps not surprising, bearing in mind the fact that this is still regarded as a delicate area by both patients and doctors, but nevertheless it is regrettable that the available information does not provide an adequate basis for analysis of this problem.

It is often a decisive factor for the individual patient. What is more, the literature deals almost exclusively with the sexual situation of the male patient. Women seem to have been forgotten in this context and it is symptomatic that the Australian author Bell, in his comprehensive review "Autonomic nervous control of reproduction: Circulatory and other factors" includes a section entitled "Clinical implications of male sexual function" but omits a corresponding analysis of female sexual function (Bell 1972). Some years later another two Australian authors conclude resignedly that "It is of interest that most attention to side effects of drugs in female sexual behaviour has focused on an exclusively female-orientated preparation, the oral contraceptive pill" (Dennstein & Burrows 1977).

## BRIEF BACKGROUND TO THE BASIC PHYSIOLOGY OF SEXUAL FUNCTION

Both the sympathetic and parasympathetic nervous systems are involved in the sexual act: in the male the autonomic activation leads to erection of the penis and mucus secretion and in the female to hyperaemia of the vulva and vagina, as well as mucus secretion. In general mental stimulation increases sympathetic activity while local stimulation leads to increased parasympathetic activity. Ejaculation and orgasm are

governed by sympathetic nervous impulses which cause rhythmic peristalsis in the genital passages.

## SPONTANEOUS DISTURBANCES OF SEXUAL FUNCTION

When assessing the possible association between antihypertensive medication and disturbances of sexual function it is important to bear in mind that both impotence and frigidity occur spontaneously with high frequency. It has been reported that about half of all men, when directly questioned, state that they are dissatisfied with their sex lives (Lording 1978). The prevalence of impotence increases with increasing age and Lording states it to be 75% in men above the age of 60. Using a questionnaire Bulpuu et al. (1976) found that the frequency of impotence in men with untreated hypertension was 17% which may be compared with the figure of 7% in their normal controls. While failure of ejaculation did not occur at all in the control group, 7% of the untreated hypertensive men complained of this. The frequency of coitus did not differ between the groups. Typically the report contains no information about the corresponding situation in female patients, despite the fact that women accounted for more than 50% of the population studied.

## INFLUENCE OF HYPOTENSIVE DRUGS ON SEXUAL FUNCTION

Bulpuu et al. (1976) also investigated the frequency of impotence and failure of ejaculation in treated hypertensive men and found higher frequencies (25% and 26% respectively) compared to untreated hypertensive men and normal controls. Secondary impotence, i.e. failure of erection in men who had previously been able to achieve coitus, was formerly a frequent phenomenon during treatment with ganglion blocking drugs. This side effect may also occur with other sympathetic inhibitors, such as bethanidine, gua-

Nihsson A, Hansson B-G & Hökfelt B. Beta-blockers and lipid metabolism. *Br Med J* 2: 126, 1977

Shaw J, England J D F & Hua A S P. Beta-blockers and plasma triglycerides. *Br Med J* 1: 986, 1978

Tanaka N, Sakaguchi S, Oshige K, Nāmura T & Kanehisa T. Effect of chronic administration of propranolol on b. protein composition. *Metabolism* 25: 1071-1075, 1976

Waal-Manning H J & Simpson F O. Beta-blockers and lipid metabolism. *Br Med J* 2: 705, 1977

## DISCUSSION

### *Callie Bengtsson*

As a complement to this paper I would like to describe what has happened to women receiving  $\beta$ -blockers and diuretics respectively in the population sample we are presently studying in Gothenburg. About 39 women have during the six year period between the studies 1968-1969 and 1974-1975 been put on diuretics and roughly 50 women have in the meantime been placed on  $\beta$ -blocking therapy. We have compared the total number of women examined at both occasions. There was no change in total cholesterol levels neither in those receiving diuretics nor in those treated with  $\beta$ -blockers although some increase was noted in the whole material. With regard to triglycerides we observed an increase of 0.1 mmol/l in the whole material and an increase of 0.35 mmol/l in those given  $\beta$ -blockers, i.e. a change of 0.25 mmol/l with a possible slight decrease of 0.1 mmol/l in those receiving  $\beta$ -blockers.

### *Stephan Rössner*

Were there any fluctuations in body weight in these women?

### *Callie Bengtsson*

All changes in body weight were similar in the various groups.

### *Arvid Eliasson*

At the Ninth Nordic Hypertension Meeting in April 1978 preliminary data from the Oslo survey dealing i.a. with the HDL fraction were presented. Significantly lower values were observed in patients treated with the combination hydrochlorothiazide + propranolol when compared to similar groups given hydrochlorothiazide alone or in combination with methyl dopa. Body weight was stable during three years but diet or smoking habits were not checked.

# NEGATIVE CONSEQUENCES OF REDUCTION OF BLOOD PRESSURE - INFLUENCE ON SEXUAL FUNCTION

Rune Samnerstedt

Although it has long been known that treatment with antihypertensive drugs may have an adverse effect on sexual function, and these side effects have been a common phenomenon ever since the days of the ganglion blockers, the otherwise so voluminous hypertension literature contains little information on this point. This is perhaps not surprising, bearing in mind the fact that this is still regarded as a delicate area by both patients and doctors, but nevertheless it is regrettable that the available information does not provide an adequate basis for analysis of this problem, which is often a decisive factor for the individual patient. What is more, the literature deals almost exclusively with the sexual situation of the male patient. Women seem to have been forgotten in this context and it is symptomatic that the Australian author Bell in his comprehensive review "Autonomic nervous control of reproduction: Circulatory and other factors" includes a section entitled "Clinical implications of male sexual function" but omits a corresponding analysis of female sexual function (Bell 1972). Some years later another two Australian authors conclude resignedly that "It is of interest that most attention to side effects of drugs in female sexual behaviour has focused on an exclusively female-orientated preparation, the oral contraceptive pill" (Demmerstein & Barrow 1977).

## BRIEF BACKGROUND TO THE BASIC PHYSIOLOGY OF SEXUAL FUNCTION

Both the sympathetic and parasympathetic nervous systems are involved in the sexual act. In the male the autonomic activation leads to erection of the penis and mucus secretion and in the female to hyperaemia of the vulva and vagina, as well as mucus secretion. In general mental stimulation increases sympathetic activity while local stimulation leads to increased parasympathetic activity. Ejaculation and orgasm are

governed by sympathetic nervous impulses which cause rhythmic peristalsis in the genital passages.

## SPONTANEOUS DISTURBANCES OF SEXUAL FUNCTION

When assessing the possible association between antihypertensive medication and disturbances of sexual function it is important to bear in mind that both impotence and frigidity occur spontaneously with high frequency. It has been reported that about half of all men, when directly questioned, state that they are dissatisfied with their sex lives (Lording 1978). The prevalence of impotence increases with increasing age and Lording states it to be 75% in men above the age of 60. Using a questionnaire, Bulpitt et al. (1976) found that the frequency of impotence in men with untreated hypertension was 17% which may be compared with the figure of 7% in their normal controls. While failure of ejaculation did not occur at all in the control group, 7% of the untreated hypertensive men complained of this. The frequency of coitus did not differ between the groups. Typically the report contains no information about the corresponding situation in female patients, despite the fact that women accounted for more than 50% of the population studied.

## INFLUENCE OF HYPOTENSIVE DRUGS ON SEXUAL FUNCTION

Bulpitt et al. (1976) also investigated the frequency of impotence and failure of ejaculation in treated hypertensive men and found higher frequencies (25% and 26% respectively) compared to untreated hypertensive men and normal controls. Secondary impotence, i.e. failure of erection in men who had previously been able to achieve coitus, was formerly a frequent phenomenon during treatment with ganglion blocking drugs. This side effect may also occur with other sympathetic inhibitors, such as betanidine, gua-

nethidine, methyldopa, clonidine and reserpine. Thus, Bulpitt & Dollery (1973) reported impotence in 67% of men treated with bethandine and 54% of men treated with guanethidine. Patients treated with diuretics or spironolactone may also occasionally complain of this symptom. *Failure of ejaculation* is above all a characteristic side effect of ganglion blocking agents but may also occur with other sympathetic inhibitors. Thus Bulpitt & Dollery (1973) reported failure of ejaculation in six out of 10 men with guanethidine and in 7 out of 17 treated with bethandine. *Retrograde ejaculation* caused by paralysis of the internal bladder sphincter may occur during treatment with postganglionic sympathetic inhibitors such as bethandine and guanethidine, leading to what has been called "dry run". As already indicated, *frigidity* and *failure of orgasm* in women during antihypertensive treatment does not seem to have been studied in any detail.

It may however be assumed on good grounds that antihypertensive drugs cause disturbances of sexual function in women too.

## FINAL COMMENT

In view of the possible serious consequences of disturbance of sexual function for the individual and his or her social life, this side effect of antihypertensive drugs merits closer attention than it has probably received up to now. This may be achieved by actively questioning patients treated with these drugs concerning changes in their sex lives and if evidence of disturbance of sexual function is found adapting the treatment accordingly. This can probably best be achieved by altering the patient's medication rather than by intermittent withdrawal of suspected antihypertensive drugs, e.g. over the weekend as has been suggested by British authors.

## REFERENCES

- Bell C. Autonomic nervous control of reproduction: circulatory and other factors. *Pharmacol Rev* 24: 657-736 1972.
- Bulpitt CJ & Dollery CT. Side effects of hypotensive agents evaluated by a self-administered questionnaire. *Br Med J* 3: 485-490 1973.
- Bulpitt CJ, Dollery CT & Carne S. Change in symptoms of hypertensive patients after referral to hospital clinic. *Br Heart J* 38: 121-128, 1976.
- Deenenstein L & Burrows GD. Sexual side effects of drugs. *Med J Aust* 2: 877 1977.
- Lording DW. Impotence: Role of drug and hormonal treatment. *Drugs* 15: 144-150, 1978.

## DISCUSSION

Stephan Rössner

At The Annual General Meeting of the Swedish Society of Medical Sciences 1977 we reported the results of a questionnaire to about 50 post myocardial infarction patients, attempting to evaluate their sexual situation with regard to possible changes after the in-

farcction and concomitant drug intake. About a third of these patients were treated with B-receptor blocking drugs. Our questionnaire did not reveal any drug-related alterations in the quality of sexual life (Näsen & Rössner 1978).

## REFERENCE

- Näsen H & Rössner S. Sexual activity after myocardial infarction - an interview study. *Läkartidningen*. In press 1978 (Swe).



# FETAL EFFECTS OF ANTIHYPERTENSIVE DRUGS

Per Lundborg

This presentation will be very brief and concentrate on a few points of general interest.

First, most doctors and pregnant women in our country are today extremely well aware of the potential hazard for the fetus if the mother is treated with various drugs during pregnancy, at least during the first trimester. Therefore, the question often is raised, whether the optimal treatment for the mother has to be withheld in favour of the fetus, or if the mother should be treated, thereby risking adverse effects on the fetus.

It has to be stated, I think, that in many situations the best for the fetus as well as for the mother is an adequate treatment of serious disease.

Secondly I would like to point out that the placenta cannot be considered an organ whose prime function is to protect the fetus against injury and infection, providing a physical barrier to the passage of noxious substances from mother to fetus.

In this sense the term "placenta barrier" must be considered a myth. It seems unlikely that a living cell membrane could be absolutely impermeable to any compound. On the contrary it is now believed that any substance found in the maternal or fetal blood should be able to penetrate the placenta to some extent unless it is destroyed or altered during passage (Moya & Thorndike 1962).

The important question is not whether a given substance does or does not pass the so-called placenta barrier but the rate and mechanism of transfer involved.

## THE TRANSPORT MECHANISMS

The basic mechanism by which substances may cross the placenta are the same as those of other biological membranes, they have been reviewed in detail by several authors (e.g. Page 1957; Moya & Thorndike 1962;

Ginsburg 1971). They may be considered as with other natural membranes, under four main headings – simple diffusion, facilitated diffusion, active transport and special processes. Only simple diffusion and active transport will be briefly considered here.

### Simple diffusion

In this instance substances cross the placenta from regions of higher to lower concentration so as to equalize concentrations on either side of the barrier.

The rate at which placental transfer occurs by these means is thought to be governed by standard physicochemical considerations. One would therefore expect the passage of lipid soluble substances across the placenta to be accelerated compared with those that are less fat soluble.

### Active transport across a membrane

This implies molecular transfer against an electrochemical gradient and must entail the expenditure of metabolic energy. This mechanism is responsible for the transfer of vitamins, amino acids, and essential ions such as calcium from mother to the fetus. Amino acid analogues like  $\alpha$ -methyl-dopa, can similarly be expected to utilize this mechanism and also to compete with other amino acids for transfer sites.

Irrespective of the transport mechanism utilized most pharmacologically active compounds given to the mother pass from the mother's blood to the fetal blood.

At acute drug administration the rate of transfer determines the maximal drug concentration reached in the fetal blood. At drug administration for a long period, as is the case in antihypertensive therapy, also drugs passing at a very slow rate can be expected to reach high concentrations in the fetal blood.

## MORPHOLOGIC AND FUNCTIONAL EFFECTS ON THE FETUS

Drug effects on the fetus are of two major types. Early in pregnancy during formation of the organ systems, the primary concern is morphologic abnormalities (i.e. congenital anomalies). Later in pregnancy functional considerations are of greater significance and during delivery such factors as respiratory depression of the neonate and inability of the neonate to metabolize or eliminate. It should also be pointed out that although the formation of most organ systems is completed after the first trimester a vast number of neural pathways in the brain are not fully developed until late in pregnancy or after birth. The possibility has to be considered that drugs interacting with brain neurotransmission can interfere with the final development of brain transmitter systems. For example continuous treatment with dopamine receptor blocking agents during the period of rapid development of brain dopamine systems has been found to result in persistent behavioural and biochemical brain changes in the rat (Ahlenius et al 1973 Engel & Lundborg 1974). This fact has to be considered in the choice of antihypertensive therapy during pregnancy.

### ANTIHYPERTENSIVE AGENTS

Various groups of antihypertensives are listed in Table 1. Although thiazide diuretics given to the mother occasionally can induce thrombocytopenia postnatally this effect is generally reversible, and many physicians consider diuretics the first drug to be used in pregnancy hypertension.

Table 1 Anti-hypertensive agents

1. Diuretics
2. Sympathetic inhibitors
  - a) Central effect: clonidine, methyl dopa
  - b) Ganglionic blocking agents
  - c) Agents interfering with granular storage mechanisms: Reserpine, bethanidine, guanethidine
  - d) Adrenergic receptor blocking agents: Alpha-blockers, beta-blockers, Non-selective, selective
3. Vasodilators: Hydralazine

Clonidine and  $\alpha$  methyl-dopa both interfere with central adrenergic mechanisms. Although nothing has been published about harmful fetal effects of these drugs in humans these drugs could theoretically be expected to interfere with the development of adrenergic mechanisms in the brain. Ganglion blocking drugs are only of minor interest in the treatment of hypertension today. It deserves to be mentioned however that ganglion blockade in the neonatal period has been found to interfere with the development of postsynaptic neurons in the rat (e.g. Black & Geen 1973).

### OTHER ANTIHYPERTENSIVE AGENTS

Concerning reserpine, bethanidine and guanethidine, they all interfere with amine storage mechanisms in adrenergic neurons. It has been argued that bethanidine and guanethidine do not pass the placenta membranes due to low lipid solubility. This does not seem very probable (see above). All three drugs can be expected to interfere with the development of adrenergic mechanisms.

### BETA BLOCKING AGENTS

Beta-blocking drugs are not seldom used in pregnancy. There are some publications available suggesting that treatment with a non-selective beta-blocker, propranolol, may have resulted in a small placenta, intrauterine growth inhibition and postnatal hypoglycaemia and bradycardia (Fiddler 1974 Gladstone et al 1975). If these effects, at least in part, can be related to beta receptor blockade it is possible that they may be avoided by using a selective beta-blocker (Sandstrom 1978).

In addition to the intrauterine effect of beta-blockers, paediatricians have pointed out that betablockade during delivery might deprive the newborn child of the possibility to respond to hypoxic situations with increased heart rate (Hjeltner personal communication).

### HYDRALAZINE

Hydralazine, finally, has been in clinical use for many years. No reports exist to my knowledge about any adverse effects on the fetus, associated with hydralazine treatment during pregnancy.

## CONCLUSIONS

In conclusion, all drugs given to the pregnant woman for the treatment of hypertension can be expected to pass the placenta membranes and reach about the same concentration in the fetal blood as in the mother's blood. It is the author's personal view that drugs interfering with neurotransmission centrally or peripherally should be used with caution and if possible be avoided.

Thiazides and hydralazine can probably be considered relatively safe drugs. If beta-blockers are to be used beta-1 selective drugs should be preferred.

## REFERENCE

- Ahlness S, Brown R, Engel J & Lundborg P Learning deficits in 4 weeks old offspring of the nursing mothers treated with the neuroleptic drug perfluridol. *Neuropsychobiology Arch Pharmacol* 279: 31-37 1973
- Black J B & Geiss S C Trans-synaptic regulation of adrenergic neuron development: Inhibition by ganglionic blockade. *Brain Res* 63: 291-302, 1973
- Engel J & Lundborg P Receptor changes in monoamine levels and the role of tyrosine and tryptophan hydroxylases in 4 weeks old offspring of the nursing mothers treated with the neuroleptic drug perfluridol. *Neuropsychobiology Arch Pharmacol* 282: 327-334 1974
- Fiddler G I Propranolol and pregnancy. *Lancet* 2: 722-723, 1974
- Gamberg J Placental drug transfer. *Annu Rev Pharmacol* 11: 387-408, 1971
- Gladstone G R, Hordof A & Orensky W M Propranolol administration during pregnancy: effects on the fetus. *J Pediatr* 86: 962-964 1975
- May F & Thorndike V Passage of drugs across the placenta. *Am J Obstet Gynecol* 84: 1778-1793, 1962
- Page E W Transfer of materials across the human placenta. *Am J Obstet Gynecol* 74: 705-715 1957
- Sandström B Effects of the selective beta-blocker metoprolol on hypertension during pregnancy. *Br J Obstet Gynecol*. In press 1978

## DISCUSSION

Morts Henning:

I would like to have your opinion about the placental transfer of bethandine and guanethidine since these drugs are poorly absorbed from the gut and are said not to pass the blood-brain barrier.

Per Lundborg:

This is true also of skeletal muscle relaxants like curare but there are reports of muscular paralysis in children delivered by mothers treated with curare-like drugs for tetanus. In my opinion placental transfer is only question of time.

Hans Lundholm:

We have determined serum levels of atenolol in 7 pairs of mothers and children, umbilical blood samples were taken immediately post partum. There were no

significant differences in atenolol levels between or within pairs. We have also examined hydralazine under similar conditions in 5 pairs, observing a higher concentration in the child than in the mother. In one patient receiving hydralazine 150 mg daily significant concentrations of the drug were found in breast milk.

Morts Henning:

It has been said that atenolol does not appreciably pass membranes of the placental or blood-brain barrier type but this would appear not to be true in the long term situation.

Per Lundborg:

It might be noted that mother and infant have different clearance of atenolol, which is the reason for the

## MORPHOLOGIC AND FUNCTIONAL EFFECTS ON THE FETUS

Drug effects on the fetus are of two major types. Early in pregnancy during formation of the organ systems, the primary concern is morphologic abnormalities (i.e. congenital anomalies). Later in pregnancy functional considerations are of greater significance, and during delivery such factors as respiratory depression of the neonate and inability of the neonate to metabolize or eliminate. It should also be pointed out that although the formation of most organ systems is completed after the first trimester a vast number of neural pathways in the brain are not fully developed until late in pregnancy or after birth. The possibility has to be considered that drugs interacting with brain neurotransmission can interfere with the final development of brain transmitter systems. For example continuous treatment with dopamine receptor blocking agents during the period of rapid development of brain dopamine systems has been found to result in persistent behavioural and biochemical brain changes in the rat (Ahlenius et al 1973 Engel & Lundborg 1974). This fact has to be considered in the choice of antihypertensive therapy during pregnancy.

### ANTIHYPERTENSIVE AGENTS

Various groups of antihypertensives are listed in Table I. Although thiazide diuretics given to the mother occasionally can induce thrombocytopenia postnatally this effect is generally reversible and many physicians consider diuretics the first drug to be used in pregnancy hypertension.

Table I Anti-hypertensive agents

- |  |                |
|--|----------------|
| 1 Diuretics  |                |
| 2 Sympathetic inhibitors                               |                |
| a) Central effect: clonidine, methyl dopa              |                |
| b) Ganglionic blocking agents                          |                |
| c) Agents interfering with granular storage mechanisms |                |
| Reserpine, bethanidine, guanethidine                   |                |
| d) Adrenergic receptor blocking agents                 | Alpha-blockers |
|  | Beta-blockers  |
|  | Non-selective  |
|  | selective      |
| 3 Vasodilators: Hydralazine                            |                |

Clonidine and  $\alpha$  methyl-dopa both interfere with central adrenergic mechanisms. Although nothing has been published about harmful fetal effects of these drugs in humans these drugs could theoretically be expected to interfere with the development of adrenergic mechanisms in the brain. Ganglion blocking drugs are only of minor interest in the treatment of hypertension today. It deserves to be mentioned, however that ganglion blockade in the neonatal period has been found to interfere with the development of postsynaptic neurons in the rat (e.g. Black & Geen 1973).

### OTHER ANTIHYPERTENSIVE AGENTS

Concerning reserpine, bethanidine and guanethidine, they all interfere with amine storage mechanisms in adrenergic neurons. It has been argued that bethanidine and guanethidine do not pass the placenta membranes due to low lipid solubility. This does not seem very probable (see above). All three drugs can be expected to interfere with the development of adrenergic mechanisms.

### BETA BLOCKING AGENTS

Beta-blocking drugs are not seldom used in pregnancy. There are some publications available suggesting that treatment with a non-selective beta-blocker propranolol may have resulted in a small placenta, intrauterine growth inhibition and postnatal hypoglycemia and bradycardia (Fiddler 1974 Gladstone et al. 1975). If these effects, at least in part, can be related to beta<sub>2</sub> receptor blockade it is possible that they may be avoided by using a selective beta-blocker (Sandstrom 1978).

In addition to the intrauterine effect of beta-blockers pediatricians have pointed out that beta-blockade during delivery might deprive the newborn child of the possibility to respond to hypoxic situations with increased heart rate (Hjellmer personal communication).

### HYDRALAZINE

Hydralazine finally has been in clinical use for many years. No reports exist, to my knowledge, about any adverse effects on the fetus, associated with hydralazine treatment during pregnancy.

## TREATMENT OF HYPERTENSION - RISK/BENEFIT EXCERPTS OF A PANEL DISCUSSION

*Chairman and referee: Hans Dunér*

*Panel members: Lewnar Hansson, Mats Henning, Rune Samerstedt and Hans Åberg*

There is general agreement that arterial hypertension is an important risk factor for the development of ischaemic heart disease, cerebrovascular disease and renal insufficiency. With increasing levels of blood pressure the morbidity and mortality from these conditions increase and the negative effect of raised arterial pressure can be observed already in young adults. These conclusions are based on studies such as The Blood and Blood Pressure Study (1959), The Framingham Study (Kannel et al. 1970), and The Chicago Stroke Study (1974).

As regards the prophylactic effect of antihypertensive treatment on cardiac complications both the Veterans Administration Trials (1967-1970) and The Framingham Study (Kannel et al. 1970) have demonstrated that development of cardiac insufficiency can be prevented when treating high blood pressure. As regards a prophylactic effect on coronary artery disease, these investigations do not demonstrate a clear-cut beneficial effect. On the other hand recent data e.g. from Sweden (Bergholm et al. 1978) show a reduction of myocardial infarctions by 50 % in a group of middle-aged men with treated hypertension as compared to a reference group. Whether this beneficial effect was due to reduction of elevated blood pressure per se or can be attributed to the choice of treatment - 80 % of the patients were treated with beta-adrenoreceptor blocking agents - cannot be determined at the present time.

There are also solid evidence that antihypertensive treatment has a prophylactic effect on the development of cerebrovascular complications. Several retrospective investigations and in particular the prospective studies of the Veterans Administration Trials demonstrate this fact.

Regarding renal function the effect of antihypertensive treatment is best demonstrated in patients with malignant hypertension. Before the era of effective

antihypertensive therapy patients with malignant hypertension could expect only a short period of survival, the cause of death frequently being uraemia. Among the trials during the 1950's which demonstrated the positive effect of antihypertensive therapy special reference was made to the trial by Kincaid-Smith et al. (1958). Today malignant hypertension is regarded as being less common than previously. One explanation could be that early treatment of essential hypertension prevents the development of the malignant phase. This view is supported by the results of the Veterans Administration Trials, which demonstrated that antihypertensive treatment prevented the development of renal damage. Also in patients suffering from chronic renal disease, e.g. chronic pyelonephritis with hypertension, investigations by Berglund et al. (1968) show an improved prognosis as an effect of antihypertensive therapy.

As regards the cost/benefit question it is difficult to make exact estimates. In one such attempt by Dahlberg (1970) the beneficial effects of the Veterans Administration Studies were applied to the Swedish population. The economic advantage for society was estimated to 200 millions U.S.-dollars annually if antihypertensive therapy was supplied to all patients with diastolic blood pressures above 100 mm mercury. In a study from the National Heart Foundation of Australia in 1970 the estimated reduction in annual mortality from cerebrovascular disease in Australia following the introduction of antihypertensive therapy comprised 2,000 individuals at an annual cost of 25 millions U.S.-dollars (Reider 1974).

From a clinical pharmacological point of view it was stressed that side effects from antihypertensive therapy in part is related to dosage. Increased knowledge, not least as regards the effects of drugs in elderly people, should make it possible to reduce the rate of side effects. A number of factors, besides the level of ar

cause a seeming difference in studies of total amounts of drugs in plasma

*Margaretha Groschinsky-Grind*

We have examined placental transfer of hydrochlorothiazide and furosemid by taking umbilical blood samples in newborn infants. Hydrochlorothiazide levels

are higher but furosemid levels are considerably lower in the child compared to the mother immediately post partum. In addition we find that amnion fluid concentrations of hydrochlorothiazide are about 7 times higher than the plasma levels of mother or child whereas amnion fluid concentrations of furosemid are lower



terial pressure as such. Influence the results of antihypertensive treatment. For this reason it is difficult to give exact cut-off points for blood pressure regarding which patients need antihypertensive treatment or not. In the individual case the physician always has to calculate with a number of conditions such as the general condition of the patient, his age, his possibilities to

adhere to the prescribed therapy, side effects, and other factors in addition to the level of his blood pressure.

However, with all these limitations in mind there was unanimous agreement in the panel that the benefits of antihypertensive therapy far outweigh the negative aspects of such treatment. The cost/benefit aspect is certainly also a very positive one.

## REFERENCES

- Bengtsson U, Högdahl A M & Flood B. Chronic non-obstructive pyelonephritis and hypertension. A long term study. *Q J Med* 27: 361-377, 1968.
- Berglund G, Wilhelmsson L, Sannerstedt R, Hansson L, Andersson O, Silverstam R, Wedel H & Wikstrand J. Coronary heart disease after treatment of hypertension. *Lancet* 1: 1-5, 1978.
- Dahlberg L. Vad kostar de vanligaste hypertoni-relaterade sjukdomarna samhället? Omhändertagande av hypertoni/74 pp 15-31. Eds. G Berglund & L Werkb. A Lindgren & Söner AB. Mölndal 1975.
- Kannel W B, Wolf P A, Verter J & McNamara P M. Epidemiologic assessment of the role of blood pressure in stroke. The Framingham Study. *JAMA* 214: 301-310, 1970.
- Kincaid Smith P, McMichael J & Murphy E A. The clinical course and pathology of hypertension with papilloedema (malignant hypertension). *Q J Med* 27: 117, 1958.
- Reader R. Hypertension and the community. *Acta Med Scand suppl* 576: 83-91, 1975.
- Shekelle R B, Ostfeld A M & Hawkins Jr H L. Hypertension and risk of stroke in an elderly population. *Stroke* 5: 71-75, 1974.
- The Build and Blood Pressure Study. Society of actuaries, vol 1. Chicago 1959.
- Veterans Administration Cooperative Study Group on Antihypertensive Agents. Effects of treatment on morbidity in hypertension. Results in patients with diastolic blood pressures averaging 115 through 129 mm Hg. *JAMA* 202: 1028-1034, 1967.
- Veterans Administration Cooperative Study Group on Antihypertensive Agents. Effects of treatment on morbidity in hypertension. II. Results in patients with diastolic blood pressure averaging 90 through 114 mm Hg. *JAMA* 213: 1143-1152, 1970.



# Acta Medica Scandinavica

Supplementum 629

## Hemoglobin fortification of food and prevention of iron deficiency with heme iron

By Peter Reizenstein



# **Acta Medica Scandinavica**

**Supplementum 629**

## **Hemoglobin fortification of food and prevention of iron deficiency with heme iron**

**By Peter Reizenstein**

# Acta Medica Scandinavica

originally published as *Nordiskt Medicinskt Arkiv* was founded in 1869 by Professor Axel Key MD. In 1901 (from volume 34) this journal was divided into a medical and a surgical section. Since 1919 (from volume 52) the medical section has been published under the name of *Acta Medica Scandinavica*.

## *Acta Medica Scandinavica*

publishes papers on general medicine mainly from Denmark, Finland, Iceland, Norway, Sweden and the Netherlands. Short preliminary reports (not exceeding two pages) will be published at short notice. The papers are published in English, French or German. *Acta Medica Scandinavica* is published on a non-profit basis.

## *Subscriptions*

to *Acta Medica Scandinavica* (two volumes of six numbers each annually) include free supplements to the current volumes.

## *Subscription Rates*

Per annum = two volumes.

In Denmark, Finland, Iceland, Norway, Sweden and the Netherlands Sw. cr. 356, incl. postage. Swedish subscribers add VAT. Other countries: Sw. cr. 405 incl. postage.

## *Chief Editor*

Professor Jan G. Waldenström MD  
*Acta Medica Scandinavica*  
Kungsgatan 54  
S-111 35 Stockholm, Sweden

## *Editorial Office*

*Acta Medica Scandinavica*  
Kungsgatan 54  
S-111 35 Stockholm, Sweden  
(All correspondence concerning manuscripts and editorial matters)  
Telephone 08/21 77 63

## *Subscription Distribution and Advertising*

The Almqvist & Wiksell Periodical Company  
Gamla Brogatan 26 Box 62  
S-101 20 Stockholm 1 Sweden

## *Printers*

Almqvist & Wiksell  
S-751 81 Uppsala, Sweden

From Division of Hematology Department of Medicine  
Karolinska Hospital 104 01 Stockholm, Sweden.

## **Hemoglobin fortification of food and prevention of iron deficiency with heme iron**

**By Peter Reizenstein**



# Contents

## Chapter I

### PREVENTION OF IRON DEFICIENCY WITH HEMOGLOBIN-IRON A REVIEW OF STUDIES OF THE ABSORPTION OF HEME AND NON-HEME IRON

#### Abstract 7

Introduction 7

Correlation between the intake of non-heme iron and iron deficiency 8

Prevalence of iron deficiency 8

Prevalence of manifest iron deficiency anemia 8

Latent iron deficiency 9

Absorption of non-heme iron 10

Efficacy of fortification with non-heme iron in preventing iron deficiency 11

Alternative preventive methods 11

Negative effects of iron fortification: Population groups at risk of side effects from iron fortification 12

Correlation between the intake of heme iron and iron deficiency 14

Meat intake and iron deficiency 14

Comparison between the absorption of heme and non-heme iron 14

Conclusions 15

References 16

## Chapter II

### HEMOGLOBIN FORTIFICATION OF FOOD ABSORPTION OF HEMOGLOBIN AND NON-HEME IRON

#### Abstract 21

Introduction 22

Methods of absorption measurements and preparation 22

Preparation of radio-active hemoglobin 22

Subjects 23

Dose-response 23

Heme and non-heme iron absorption 23

Hemoglobin stability during baking 23

Pharmaceutical hemoglobin preparations 23

Hemoglobin in meat products 24

Hemoglobin in bread 24

Bleached hemoglobin a protein extender 24

Results 24

Response of absorption to hemoglobin dose 24

Comparison of heme and non-heme iron absorption 25

Hemoglobin iron absorption from bread 25

Hemoglobin stability during baking 25

Hemoglobin iron absorption from meat products 25

Iron absorption from bleached hemoglobin 25

Effect of the pharmaceutical hemoglobin preparation	28
Conclusions	28
References	30

### Chapter III

#### INTESTINAL ABSORPTION OF HEME IRON IN MAN

Abstract	31
Introduction	31
Materials	32
Methods of separating heme and globin of characterizing porphyrins and of preparing heme iron	32
Separation of heme hemin or hematin from globin	32
Characterization of porphyrin	33
Hemin-iron preparations	33
Results	33
Absorption of hemoglobin iron	33
Characterization of porphyrin	33
Absorption of hemin from ordinary capsules	33
Absorption of hemin in enteric coated capsules	34
Absorption of hemin in solutions	34
Discussion	34
Comparison values for the absorption of non-hemin iron	34
References	43

### Chapter IV

#### NUTRITIONAL VALUE OF BLOOD PROTEINS

Abstract	45
Chemical score	45
Evaluation of formulated foods and protein extenders	45
References	46

ACKNOWLEDGMENTS	47
-----------------	----



## Introduction

Even in 1979 there is much malnutrition in the world. A few years ago, anemia was ranked by the WHO Regional office for Africa as one of the five most important medical problems in that region, and here iron deficiency plays a major role.

Moreover, about 1/4 of the population in Africa and the Far East are undernourished. The reasons for this were studied by The World Food Conference in Rome in 1974. It was found that, in addition to distribution problems and economic problems a real food shortage is a major reason. Therefore the utilization of residues like cattle hemoglobin appears logical and useful. This is the motive for the present monograph.

The present results of a comparison of the absorbability of heme iron and vegetable iron suggest that it could be useful to utilize cattle hemoglobin in the prevention of iron deficiency. The present results of studies of the nutritional value of meals containing blood proteins suggest that it could also be useful to utilize cattle blood proteins as protein extenders and a source of energy.



## Chapter I

# Prevention of iron deficiency with hemoglobin iron

## A review of studies of the absorption of heme and non heme iron

### Abstract

The relative roles of non-heme and heme iron in preventing iron deficiency are reviewed. While it has been difficult to demonstrate in different population groups, any correlation between the intake of non-heme iron and iron deficiency, such correlations have been found between the intake of meat and iron deficiency. Alternative interpretations of these findings are discussed.

The absorption of non-heme iron under experimental and physiological conditions is reviewed. Under experimental conditions and in acute iron deficiency absorption is invariably very good, but under long-term conditions of prophylaxis absorption is reduced and side effects lead to non-compliance of patients. This suggests studies of heme iron for prophylactic purposes.

Repeated studies between 1945 and 1978 have failed to prove the efficacy of iron fortification, and some suggest that even tablets may not be efficient in the prevention of iron deficiency. Concern about possible negative effects of prophylaxis with non-heme iron has increased lately, particularly when iron tablets mask the anemia of gastrointestinal cancer. Heme iron has only a small advantage in these respects, namely that doses and the maximal absorption are lower.

In different studied meals, the heme iron absorption is usually higher than the non-heme iron absorption, probably because the absorption of non-heme iron is inhibited by several constituents of the meal.

The prevalence of iron deficiency is reviewed. It is suggested that directed prophylaxis with heme iron in tablet form, which can be directed towards at risk groups and away from groups in the gastrointestinal cancer age, tablets which can be taken with meals and without side effects should be studied as an alternative to generalized iron fortification.

### INTRODUCTION

Iron deficiency, latent and manifest, is still a relatively common problem in some of the industrialized countries and a very common one in developing countries. Several attempts to demonstrate the efficacy of non-heme iron to prevent iron deficiency have failed, and concern about possible negative effects of the extensive use of non-heme iron is increasing. It has been more difficult to demonstrate a correlation of the frequency of iron deficiency to the intake of non-heme iron than to that of heme iron. These are some of the reasons to discuss the possible use of hemoglobin iron in prevention of iron deficiency.

## Correlation between the intake of non-heme iron and iron deficiency

If non-heme iron were optimal in preventing iron deficiency a relatively good correlation between the intake of this form of iron and the prevalence of iron deficiency and anemia would be expected. It is therefore surprising that no such correlation has been found even when the intake of non-heme iron varied between 6 and 25 mg per day (Davis et al 1967). These negative findings were confirmed by Elwood (1969) in adults and by Samuelsson et al (1972) in children. On the other hand a statistically significant ( $p < 0.01$ ) correlation ( $r = +0.44$ ) could be found by Quist, Ekman and Norden (unpublished) between the total iron intake and the serum ferritin level.

These studies were all done in industrial countries but even more wide variations can be found if developing countries are included. For instance Nigeria, India, and Tanzania have average calculated intakes of non-heme iron between 27 and 41.6 mg per capita per day and yet the frequencies of anemia in these countries is considerably higher than in other countries with lower iron-intake (Reizenstein, 1974; Sood et al 1968).

Naturally this is no proof that iron deficiency is independent of the intake of non-heme iron. Obviously if the non-heme iron intake becomes extremely low iron deficiency must become a result. Also independent differences between the populations and countries compared could obscure the correlation. It is obvious that such differences exist regarding health care delivery systems, the frequency of diseases like schistosomiasis, malaria etc. or of alternative dietary deficiencies. Nevertheless it is notable that high intakes of non-heme iron may well be associated with a high prevalence of iron deficiency.

## PREVALENCE OF IRON DEFICIENCY

Manifest iron deficiency is defined as iron deficiency anemia. Anemia has often been as a hemoglobin value under the mean value minus 2 standard deviations in a normal population (Vallar et al 1971). For Norwegians in 1970 this would imply that hemoglobin under 14 g/100 ml would be pathologic in men, and under 12.5 g in women. However several investigators have used 12 g/100 ml as a border-line (Jungner 1966). Latent iron deficiency anemia is defined as a reduction in the iron content of the body. The body stores can be measured only indirectly by estimating the bone marrow iron stores or by measuring the serum ferritin, the unsaturated iron binding capacity, the serum ferritin, or the intestinal iron absorption.

### Prevalence of manifest iron deficiency anemia

In Sweden a number of studies have indicated that 20 - 25 per cent of women in the fertile age groups had iron deficiency anemia before 1966 (Waldenström, 1946; Garby 1969; Hallberg 1970; Hallberg, Hallgren, Holmänder, Högdahl and Tibblin 1969; Oddefeldt 1968). However one study (Jungner 1966) showed a frequency of only 8 per cent. In contrast to the other studies quoted here Jungner's included women older than 50 years. After 1966 a rapid decrease in the prevalence seems to have

taken place (Bengtsson et al 1977). In 1963 the mean hemoglobin in fertile women was 121 g/l. In 1968 it was 135 and in 1975 it was 136. Iron deficiency is of course much less prevalent among adult men. Only about 1 per cent have iron deficiency anemia (Jungner 1966, Tübblin et al 1968). In Denmark, studying 0.5 per cent of a county population, Damberg (1979) found anemia in 8 per cent of women in fertile age groups and in 3 per cent of young men. In old men and women, 20 per cent had anemia presumably of different origins. In Finland, 2 per cent of young men had less than 130 g and 5 per cent of young women had under 120 g haemoglobin per litre blood; 50 per cent of women lacked stainable iron. Anemia was most common in middle aged women from rural areas. Here also anemia was common in the elderly (Takkunen 1976). In Norway (Vellar 1979) 8 per cent of a small sample of men had anemia, which was found mostly in elderly men. Of women, 11.8 per cent had anemia in a "poor" and 6 per cent of women in a "wealthy" community. In England iron deficiency anemia has been found in between 12 and 25 per cent of women (Kilpatrick 1970) and in 2 - 8 per cent of men.

In developing countries iron deficiency anemia may be much more common and found in up to 60 - 80 per cent of adult women and children (Good Barney Ramang-anawami 1969, Stott 1960, Reitenstein 1974). It has been shown that iron deficiency anemia reduces the physical working capacity if the work load is nearly maximal (Jacobs 1977a).

### Latent iron deficiency

Normal body iron reserves vary between 1 and 2 g. A minimum of 0.5 g has been considered to be necessary to meet iron losses during pregnancy etc. (Finch 1970). However, it is difficult to relate the size of iron stores to the measurable diagnostic findings regarding transferrin saturation, stainable bone marrow iron or intestinal iron absorption. When the reserves are low latent deficiency occurs.

It is debatable whether latent iron deficiency causes symptoms. In un-controlled studies iron treatment may improve non-specific signs such as tiredness or head aches (Jasinsky 1949 and 1950) but in controlled studies it is difficult to show significant effects (Beutler, Larab and Garney 1960, Morrow et al, 1968, Elwood, Waters, Green, Sweetnam and Wood 1969, Flwood et al 1966, Elwood et al 1970). A possible association between iron deficiency and the secretion of nor-adrenalin, or the mono-aminooxidase metabolism has been suggested (Jacobs 1977). It has also been suggested that iron deficiency reduces immunocompetence. Fewer infections in children whose iron deficiency had been treated than in the non-treated, and defective lymphocyte transformation in iron deficient patients suggested this (Jacobs 1977). So far the only certain signs of latent iron deficiency are decreases of iron containing enzymes such as cytochrome-oxidase (Fairbanks et al 1971, Jacobs 1961, Beutler et al 1960). Ribonuclease may also be iron dependent (Jacobs 1977) and this may explain probably defective proliferation of, e.g. epithelial cells in iron deficiency.

There are very few studies of the prevalence of latent iron deficiency, but almost all blood donors have latent deficiency (Höglund 1969, Liedén 1973, Magnusson et al 1976). Of women in the fertile age groups, about 40 per cent had increased iron absorption in 1968, and the corresponding figure in adolescent men is 15 per cent (Höglund 1969).

Höglund et al 1970) In 1975 however only 16 - 18 per cent of women had signs of latent iron deficiency in the form of an increased iron binding capacity without anemia (Bengtsson 1979) and 25 per cent of the women lacked stainable bone marrow iron

## ABSORPTION OF NON-HEME IRON

Numerous studies have demonstrated that single doses of iron in the form of ferrous sulfate are well absorbed when given on a fasting stomach particularly by patients with iron deficiency (Bothwell et al 1962 Brise et al 1962 Pritchard et al 1964 Hallberg et al 1967 Callender et al 1969 Helander et al 1969 Höglund et al 1969 Reizenstein et al 1973 Norrby 1974 Reizenstein et al 1975) However it is doubtful whether such experimental results are relevant for the prophylaxis of iron deficiency

Under experimental conditions single doses of iron are taken on a fasting stomach, whereas prophylaxis must be performed during prolonged times

Administration at least of appreciable amounts of iron for long times on a fasting stomach has frequently appeared to be difficult There are several reasons for this Firstly prophylaxis is usually given to subjects without symptoms of iron deficiency and for this reason between-meal-medication may be forgotten Even patients with symptoms frequently forget medication (Sackett et al 1975 Malahy 1966 Bengtsson 1972 Gatlery 1968 Stewart and Cluff 1972 Malahy 1966 Laholai and Berry 1969 Schwartz et al 1962 Watkins et al 1967 Davies 1968) Secondly if prophylaxis is attempted with large iron doses side effects will interfere with continued medication If prophylaxis of a large population who have little symptoms of iron deficiency to remind them of taking drugs or to make them endure side effects is to be practicable and if prophylaxis is to be continued for many years forms must be devised where treatment can be free of side effects and where tablets can be taken with meals when they are remembered However non-heme iron is frequently given to subjects with the intent of preventing manifest deficiency If the iron is to be given with meals and if the dose is kept low enough to prevent side effects absorption may become unsatisfactory Again there are several reasons for this

One reason is the inhibition of the absorption of non-heme iron by phytates phosphates and other components of the food (Höglund et al 1969 Moore 1969 Elwood et al 1970 Layrisse et al 1971 Rasmussen et al 1972 Martinez-Torres et al 1973 Rasmussen 1975 Reizenstein et al 1975 a) The absorption of from 15 to 20 mg food-iron in latent iron deficiency may reach 20 per cent of the food iron (Finch et al 1950 Crosby et al 1963 Weinfeldt 1965 Norrby et al 1974) at least if the iron forms a part of a meal where it is easily available (Björn-Rasmussen 1979) If the iron deficiency becomes manifest and the meal composition is still favorable to absorption, absorption may be doubled If on the other hand the meal composition is less favorable absorption may be reduced to 5 %

A second reason is the so called marginal tax effect The dose response curve of iron absorption is not linear Much less is absorbed from e.g. the additional 20 mg added for prophylactic purposes than from the initial 20 mg present in the food

A third possible inhibitor of non-heme iron absorption when iron is administered continuously may be the increased concentration of ionizable iron in the intestinal lumen (Wiglund 1969). As a final result, the absorption increase seems to correspond to only 3 % of the additional iron dose or 0.6 mg/day (Liladén 1973, Reizenstein et al 1975 a) when the iron intake is raised from, for instance 20 mg in the food to 40 mg from food and prophylactic non-heme iron. This absorption increase is frequently too small to compensate for large menstrual blood losses or for losses from repeated pregnancies or for losses from even slight intestinal hookworm infection (Reizenstein 1974). This may explain why in some developing countries iron deficiency is frequent despite iron intakes as high as 40 mg/day.

In many instances, prophylaxis with non-heme iron may be effective nevertheless. If patients remember to take tablets between meals, if they can tolerate large doses of iron, or if the blood-losses are small, this may be the case. However, there seem to be sufficiently many cases where these conditions are not met to justify the search for alternative prophylactic methods.

#### EFFICACY OF FORTIFICATION WITH NON-HEME IRON IN PREVENTING IRON DEFICIENCY

By far the greatest efforts to prevent iron deficiency have been made with the help of fortification of flour. Hundreds of millions of people in England, Scandinavia and other countries have been subjected to this form of prophylaxis. In comparison prophylactic attempts with iron tablets have been extremely limited.

However, it has been difficult to demonstrate the efficacy of iron fortification. No effect on the hemoglobin-level could be demonstrated in female mental patients (Elwood 1963) or in healthy women (Elwood et al 1971). Several early studies also failed to show any effect of iron fortification (MacKay et al 1945, Widdowson et al 1954, Harrell et al 1957). In Sweden, no decrease in the prevalence of iron deficiency anemia could be demonstrated after the introduction of iron fortification in 1944. The level of fortification was increased in 1963, but studies as late as 1965 showed no decrease in the anemia prevalence. A rapid decrease in the prevalence could then be demonstrated between 1966 and 1968, prior to the next increase in the fortification, 1970 (Bergsjö et al 1977) and prior to an improvement of fortification iron quality (Reizenstein 1977). While it is possible that the frequency decrease about 1967 could be caused, in part, by the fortification increase in 1963, no evidence for the cause-effect relationship is available.

#### ALTERNATIVE PREVENTIVE METHODS

It has been proposed that iron fortification can be replaced by oral iron medication, which can be directed to the at-risk-groups (women in fertile age groups, adolescents, blood donors, gastrectomized patients) and away from the groups at risk of iron overload (hemochromatosis, porphyria cutanea tarda, thalassemia, aplastic anemia, perhaps also stress polycythemia with hypertension and alcoholism) and away from those age groups where gastrointestinal cancer is common.

In Sweden, medication with foreseeable life-long duration, such as for instance

folic acid to patients with sprue or vitamin-B<sub>12</sub> to patients with pernicious anemia is free of charge. Iron medication may also be required for many years, since it has been demonstrated that menstrual blood losses are relatively constant during the entire fertile period (Hallberg et al 1964). Those women who have high menstrual blood losses will therefore probably require iron supplementation for several decades. Therefore, it has been proposed that iron supplementation in Sweden to women with high menstrual blood losses and gastroectomized patients be made freely available (Reizenstein 1977) as it is already to blood donors and to pregnant women.

However, Damberg (1979) has studied the effect of iron tablets containing 20 mg iron on the prevalence of anemia. He found no lower hemoglobins in those who did not than in those who stated that they did take these tablets. He also compared the average sales of iron tablets in 4 countries. The range was 1.7 mg/capita per day in England and 8.6 mg in Sweden, but apparently he could find no corresponding difference in the prevalence of anemia. Damberg (1979) also compared the average intake of fortification iron in mg/person/day (4.7 in Denmark, 8 in Sweden, 1.4 in England) without finding differences in the prevalence of anemia. His conclusion is that fortification with non-heme iron is not effective.

#### NEGATIVE EFFECTS OF IRON FORTIFICATION. POPULATION GROUPS AT RISK OF SIDE EFFECTS FROM IRON FORTIFICATION

Initially, most addition of iron to food aimed at so-called reconstitution of iron levels present in e.g. flour before sifting. Later, much higher fortification levels were used, but only recently has any sincere discussion of the possible side effects started. One has attempted to identify the groups at risk to show side effects and to discuss alternative ways of preventing iron deficiency.

Four groups have been discussed. In idiopathic hemochromatosis, where in some cases the total body iron content is of the order magnitude of 10 grams, iron deposition damages the liver, pancreas and heart. Reduction of the total body iron improves the five year survival from 33 to 89 per cent (Walker et al 1974).

In porphyria cutanea tarda, total body iron stores are increased to a lesser degree. Here also, a reduction of the total body iron decreases symptoms (Lundwall 1971). Iron absorption is increased (Reizenstein, Höglund, Landegren, Carlmark and Forsberg 1975 b).

An increased iron intake in patients with hemochromatosis or porphyria tarda causes earlier manifestations of the disease with considerable probability. So far, however, these diseases have been considered so rare that the benefit of iron fortification has been considered to exceed the damaging effects.

Lately, one has been able to find suspected iron overload in a higher number of cases than previously thought, and several authors emphasize side effects of iron fortification (Crosby 1974, Reizenstein et al 1975 c, Olsson 1979). An additional reason to view fortification critically is the fact that iron intakes in iron fortification be-



come highest in the population groups which have the least iron deficiency and possibly the highest risk of side effects namely adult men.

The possible damaging effect of iron fortification is far less certain in cardiac disease although a correlation between high hemoglobin values, high serum lipid values hypertension and cardiac disease has repeatedly been demonstrated (Elwood et al. 1970 Böttiger et al 1972)

An increased iron deposition in the liver of patients with alcoholic cirrhosis has been observed and studies of the possible liver damage resulting from iron deposition in patients with a high iron and high alcohol intake have been proposed (Reizenstein et al 1975 c) However the only population groups systematically studied in this context are the Bantu in South Africa, with a high consumption of alcohol and iron in the form of Banto-beer. The more relevant population groups in countries where iron fortification is currently used seem not to have been studied in these respects

Of all the patients with gastrointestinal cancer 85 per cent have occult blood in the stools and anemia is often the first symptom. This anemia can be masked and the diagnosis of gastrointestinal cancer can be delayed by an increased iron intake (Reizenstein et al 1975 c Reizenstein 1977) It has been calculated, that even the increased total absorption of iron resulting from iron fortification may cause relevant delays in the diagnosis in some cases (Reizenstein et al 1975 c) More effective "masking" of the anemia may result from prophylactic iron tablets. However this masking effect becomes most pronounced if iron medication is erroneously given to anemic patients with gastrointestinal cancer without preceding proper diagnosis. Recent studies suggest that such erroneous prescriptions may not be uncommon. The question should be studied if the possible masking of gastrointestinal cancer with iron becomes more common in a country where iron tablet sales are high and actively promoted

It can not be excluded that in the foreseeable future the criticism of iron fortification in its present form will increase. Evidence indicates that it is not always an efficient form of preventing iron deficiency and that it may perhaps have damaging effects more often than previously thought. There are therefore good reasons for the drug industry to look for alternative ways of preventing iron deficiency

There is no evidence yet that heme iron could mg for mg cause less potential damage than non-heme iron either in hemochromatosis porphyria cutanea tarda or gastrointestinal tumours although this has been suggested (Reizenstein et al 1975 b Hallberg 1978) However heme iron quantifies both when hemoglobin is naturally present in food, or when it is used for fortification or in tablet form, are usually much smaller than non-heme iron quantities. In consequence the maximal reported total amount of non-heme iron absorbed in manifest iron deficiency after a single administration is about 40 mg (Norris 1974) as compared to 3 - 4 mg for heme iron. Heme iron, undoubtedly suitable for the rapid administration of iron in acute deficiency but possibly suitable for long term prevention, may therefore have fewer potential negative or damaging effects than non-heme iron

Two possible explanations for the difficulty to demonstrate an effect of prophylaxis with non-heme iron must be considered. One is the particular form of non-heme iron used for fortification purposes namely so called reduced, particulate iron. It is probable that variations in the quality of this iron may make it less absorbable

follicle acid to patients with sprue or vitamin-B<sub>12</sub> to patients with pernicious anemia is free of charge. Iron medication may also be required for many years since it has been demonstrated that menstrual blood losses are relatively constant during the entire fertile period (Hallberg et al 1964). Those women who have high menstrual blood losses will therefore probably require iron supplementation for several decades. Therefore it has been proposed that iron supplementation in Sweden to women with high menstrual blood losses and gastrectomized patients be made freely available (Reizenstein 1977) as it is already to blood donors and to pregnant women.

However, Damberg (1979) has studied the effect of iron tablets containing 20 mg iron on the prevalence of anemia. He found no lower hemoglobins in those who did not than in those who stated that they did take these tablets. He also compared the average sales of iron tablets in 4 countries. The range was 1.7 mg/capita per day in England and 8.5 mg in Sweden but apparently he could find no corresponding difference in the prevalence of anemia. Damberg (1979) also compared the average intake of fortification iron in mg/person/day (4.7 in Denmark, 8 in Sweden, 1.4 in England) without finding differences in the prevalence of anemia. His conclusion is that fortification with non-heme iron is not effective.

#### NEGATIVE EFFECTS OF IRON FORTIFICATION. POPULATION GROUPS AT RISK OF SIDE EFFECTS FROM IRON FORTIFICATION

Initially, most addition of iron to food aimed at so-called reconstitution of iron levels present in e.g. flour before sifting. Later, much higher fortification levels were used but only recently has any sincere discussion of the possible side effects started. One has attempted to identify the groups at risk to show side effects and to discuss alternative ways of preventing iron deficiency.

Four groups have been discussed. In idiopathic hemochromatosis, where in some cases the total body iron content is of the order magnitude of 10 grams, iron deposition damages the liver, pancreas and heart. Reduction of the total body iron improves the five year survival from 33 to 89 per cent (Walker et al 1974).

In porphyria cutanea tarda, total body iron stores are increased to a lesser degree. Here also a reduction of the total body iron decreases symptoms (Lundwall 1971). Iron absorption is increased (Reizenstein, Högglund, Landegren, Carlmark and Forsberg 1975 b).

An increased iron intake in patients with hemochromatosis or porphyria tarda causes earlier manifestations of the disease with considerable probability. So far, however, these diseases have been considered so rare that the benefit of iron fortification has been considered to exceed the damaging effects.

Lately, one has been able to find suspected iron overload in a higher number of cases than previously thought and several authors emphasize side effects of iron fortification (Crosby 1974, Reizenstein et al 1975 c, Olsson 1979). An additional reason to view fortification critically is the fact that iron intakes in iron fortification be-

For this reason the absorption of hemoglobin iron when taken together with a fairly large number of food-stuffs and meals has been studied and compared to that of non-heme iron. The meals tested contained both meat and vegetable food. Even when hemoglobin iron was compared to ferrous sulphate in a meal consisting only of meat, hemoglobin iron was absorbed better. In almost all meals tested heme iron was absorbed between 2 and 3.6 times better than non-heme iron (Chapter II).

It has thus been demonstrated that, while non-heme iron is well absorbed under experimental conditions, it is relatively poorly absorbed under realistic nutritional conditions. This may explain why it has been difficult to demonstrate the efficacy even of high level long lasting iron fortification, and why iron deficiency is common even in countries with high intakes of non-heme iron. Hemoglobin iron, on the other hand, while less well absorbed under experimental conditions than non-heme iron is absorbed between 2 and 3.6 times better in almost all the food combinations and meals tested. When taken together with meals hemoglobin iron appears to be preferable.

## CONCLUSIONS

There are five reasons to study further the possible role of heme iron or hemoglobin iron in the prevention of iron deficiency. One is that the efficacy of non-heme iron has been difficult to demonstrate. Several studies of the fortification of flour have not shown convincing effects in terms of hemoglobin values.

A second reason is that concern exists about possible - largely still hypothetical - negative effects of generalized iron fortification.

A third reason is that wide-spread use of iron tablets containing 37 to 100 mg iron has been shown to mask blood losses from gastrointestinal tumors. Hemoglobin tablets containing only 0.4 mg iron are less risky and the possibility that they may be equally effective in preventing iron deficiency should therefore be studied.

A fourth reason is that no correlation has been found between the frequency of iron deficiency and the intake of non-heme iron, but that the heme iron intake (meat intake) does seem to show such a correlation.

The fifth reason is that hemoglobin iron, when added to some studied meals is absorbed better than non-heme iron. However, no large, controlled studies of prevention with heme iron have been published. Such studies are therefore proposed.

than iron salts (Höglund and Reizenstein 1969 Rasmussen 1975) However even fortification studies with iron salts have given controversial results (Elwood et al 1971 Stott 1960 Natvig et al 1973 Damberg 1979 Liedén 1973 Reizenstein et al 1975)

## CORRELATION BETWEEN THE INTAKE OF HEME IRON AND IRON DEFICIENCY

The difficulties to demonstrate a correlation between the intake of non-heme iron and the prevalence of anemia have been described above. However there are some observations which could indicate a possible correlation between the intake of heme iron and the prevalence of anemia.

### Meat intake and iron deficiency

Heme iron is of course found only in meat, fish and food fortified with hemoglobin. In countries with a high meat intake, such as the USA or Australia, iron deficiency anemia appears to be much less common (Reizenstein 1977) than in countries with low meat intake, such as India. Differences other than in meat intake between these countries might of course explain the difference in the anemia prevalence, but similar observations have been made in a more homogeneous population (Conrad 1970, Takkinen 1976). The decrease in the prevalence of iron deficiency anemia (Bengtsson, Tibblin 1977) noticed during the last decade in Sweden is concomitant with an increase in the meat intake (Reizenstein et al 1979). Again, however, no cause-effect relationship can be demonstrated.

The most systematic studies of the correlation between meat intake and iron deficiency have been made by Takkinen (1976) who found a statistically significant negative correlation between the unsaturated iron binding capacity in the blood and the meat intake. Men with iron deficiency anemia studied in Finland consumed 28 per cent less meat than men with normal blood values (Takkinen 1976). Together these observations suggest, but do not yet prove, that an increased meat intake may be associated with a low prevalence of iron deficiency anemia. However, besides heme iron, meat also contains factors promoting the absorption of non-heme iron (Martinez - Torres et al 1971, Martinez - Torres et al 1973, Layrisse et al 1968). It is also possible, of course, that the increased heme-iron intake in meat eaters contributes to the prevention of iron deficiency. Therefore further studies of the reason for the possible negative correlation between meat intake and iron deficiency are required.

## COMPARISON BETWEEN THE ABSORPTION OF HEME AND NON-HEME IRON

The absorption of hemoglobin iron under experimental conditions 19, in fasting subjects, has been studied repeatedly (Turnbull et al 1962, Hallberg et al 1967, Callender et al 1957, Layrisse et al 1969) and been found to be between 50 and 100 per cent of that of ferrous iron. However, neither desferrioxamine nor other studied inhibitors of the absorption of ferrous iron can inhibit hemoglobin iron absorption. Similarly, a normal meal inhibits the absorption of non-heme iron (Lindell et al 1963, Conrad et al 1967) but not that of hemoglobin iron (Reizenstein et al 1973, Reizenstein et al 1975, Chapter II).

- Elwood, P C Waters, W and Sweetnam P Clin. Sci 40 31 1971
- Elwood P C Mahler R. Sweetnam, P Moore F and Walsby E Lancet 1:649 1970
- Elwood, P C Waters W E Green W J W Sweetnam P M and Wood, M M.J of Chron Dis 21 615 1969
- Elwood P C Benjamin, L T Fry F A Ekins J Brown, D A DeKock, P C and Shah, J V Amer J Clin. Nutr 23 1287 1970
- Fairbanks V F Fahey J L and Beutler E In Clinical disorders of iron metabolism Grune & Stratton, New York and London, 1971
- Finch C A In: Iron deficiency pathogenesis clinical aspects therapy Hallberg L Harwerth, R -C Vanotti A Eds Academic Press London New York 1970 p 163
- Finch, S Haskins, D and Finch, C A J Clin. Invest 28 1078 1950
- Garby L Acta Med Scand 165:113 1969
- Garby L Ironell L and Werner L Acta Soc Med 72 21 1967
- Galley 1968, cited from "Lack of compliance with doctors orders A review" Folia Ciba Geigy (In Swedish) 1 2 1977
- Hallberg L In Iron deficiency pathogenesis clinical aspects therapy Hallberg L Harwerth, H -C Vanotti A Eds Academic Press London New York 1970 p 483
- Hallberg L Paper read to symposium on iron deficiency Stockholm 1979 Nörlingsforskning 23 69 1979
- Hallberg L and Nilsson, L. Acta Obst et Gynec Scand 43:352 1964
- Hallberg L and Solvell, L. Acta Med Scand 181 325 1967
- Hallberg L Hallgren, L Hollander A Högdahl, A -M and Tibblin, E, In Occurrence causes and prevention of nutritional anaemias, p 19 1969 Blix, G Ed. Swedish nutrition foundation, Almqvist & Wiksell, Uppsala.
- Harris, L Hoene A and Johnston, F A Am diet ass 33:1010 1957
- Heinrich, H C Bartels H Galibe E E Meincke N Nass W P and Whang D H Klin. Wochr 47:309 1969
- Höglund, S Acta Med Scand 186:487 1968
- Höglund S and Reizenstein, P Blood 34:496 1969
- Höglund S Klu, L and Liedén, B Acta Haemat. 44 193 1970
- Jacobs A Lancet 2 1331 1961
- Jacobs A Brit Med J 4:206 1972
- Jacobs A Disorders of iron metabolism In: Recent advances in hematology p 1 1971 a

## REFERENCES

- Bengtsson 1972 cited from 'Lack of compliance with doctor's orders A review  
Folia Ciba Gelgy (In Swedish) 1:2 1977
- Bengtsson C In Scand Symp on Iron Deficiency and Iron Treatment Gothenburg  
1977 L Hallberg Ed Publ by H&Ssle Co Malmö 1979
- Bengtsson C Garby L Hallberg L Lennartsson J Rossander L  
and Tibblin E *Läkartidningen* 74 1719 1977
- Bentler E Larsh S and Gurney C W *Ann Int Med* 52 378 1960
- Bothwell T H Cook, T and Finch C A In Iron Metabolism Little  
Brown & Co Boston 1962
- Björn-Rasmussen, E 1978 - see Rasmussen
- Brise H and Hallberg, L *Acta med Scand Suppl* 376 1 1962
- Böttiger L E and Carlsson, L A *Brit Med J* 3 731 1972
- Callender S and Warner G *Brit Med J* 4 532 1969
- Callender S Mallett B and Smith M *Brit J Haematol* 3 186 1957
- Carlmark, B and Reizenstein, P In *Symposium on Iron Fortification*  
Sw Food Admin Uppsala 1978 In press in 'Our food (Vår Föda in  
Swedish) Publ by Sw Food Admin Uppsala
- Conrad M E In Iron deficiency pathogenesis clinical aspects therapy  
Hallberg L Harwerth H -C Vanotti A Eds Academic Press  
London - New York 1970 p 87
- Conrad M E Benjamin B J Williams H L and Foy A L *Gastroentero-  
logy* 53 5 1967
- Crosby W H *New Engl J Med* 290 1435 1974
- Crosby W H Conrad Jr M E and Wheby M S *Blood* 22 429 1963
- Damberg S E In *Scand Symp on Iron Deficiency and Iron Treatment*  
Gothenburg 1977 Hallberg L Ed Publ by H&Ssle Co Malmö 1979
- Davies 1968 cited from "Lack of compliance with doctors orders A review  
Folia Ciba Gelgy (In Swedish) 1:2 1977
- Davies R Jacobs A and Rivlin, R *Brit Med J* 3 711 1967
- Elwood P C *Brit. Med J* 1 224 1963
- Elwood P C In Occurrence causes and prevention of nutritional anemias  
loc cit p 556 1969 Bliz Ed Swedish nutrition foundation Almqvist  
& Wiksell Uppsala
- Elwood P C *Chron Dis* 21 615 1969 *Brit Med J* II 254 1970
- Elwood P C and Hughes H *Brit Med J* II 254 1970
- Elwood P C and Wood M M *Brit J Prev Soc Med* 20 172 1966

- Rasmussen E Sw J Nutr Res (Näringsforskning in Swedish) 19 Suppl 11 p 46 1975
- Rasmussen, E In: Scand. Symp on Iron Deficiency and Iron Treatment, Gothenburg 1977 Hallberg L Ed Publ by Håssle Co, Mölndal 1979
- Rasmussen E Hallberg L and Walker R Amer J Clin Nutr 25:317 1972
- Reizenstein, P Carlmark, B Ehn, L Forsberg K Höglund, S and Terpstra T In: Radioactive tracer techniques for the study of gastrointestinal absorption. Int. Atom Energy Ag Techn Document 185 66, 1973
- Reizenstein, P World Health Organization report to Government of United Republic of Tanzania AFR/NUT 73 1974
- Reizenstein P Carlmark, B Ehn, L and Forsberg K In: Iron Metabolism and its disorders H Kief Ed Publ Excerpta Medica, Workshop Conf Bochat 3 175, 1975
- Reizenstein P Ehn, L Forsberg K Höglund S and Liedén, G Näringsforskning (in Swedish) 19 Suppl 11 p 39 1975 a
- Reizenstein, P Höglund, S Landegren, J Carlmark, B and Forsberg K Acta Med Scand 198: 95, 1975 b
- Reizenstein, P Höglund, S and Landegren, J Sw J Nutr Res (Näringsforskning in Swedish) 19 Suppl 11 p 17 1975 c
- Reizenstein, P Sw J Pharm (Svensk Farmaceutisk Tidskrift, in Swedish) 81: 385 1977
- Reizenstein P Carlmark, B Ehn L and Siesby H In: Scand Symp on Iron Deficiency and Iron Treatment, Gothenburg 1977 L Hallberg Ed Publ by Håssle Co Mölndal 1979
- Seckat et al 1975, cited from "Lack of compliance with doctors orders A review" Folia Ciba Geigy (in Swedish) 1: 2 1977
- Samuelsson, O and Sjölén S Acta Paediatr Scand 61: 83 1972
- Schwartz et al 1982 cited from "Lack of compliance with doctors orders A review" Folia Ciba Geigy (in Swedish) 1: 2 1977
- Sood S Barney L and Ramangaswami L In Occurrence causes and prevention of nutritional anemias p 36 1969 O Blitt, Ed Swedish nutrition foundation, Almqvist & Wiksell Uppsala.
- Stewart and Cluff 1972 cited from "Lack of compliance with doctors orders A review" Folia Ciba Geigy (in Swedish) 1: 2 1977
- Stott, R Bull World Health Org 23 781 1960
- Takkunen, H Scand J Haematol Suppl 125, p 1 1978
- Tibblin, S and Jungner J Läkartidningen 63: 2802 1966
- Turnbull A Clifton, F and Flach, C J Clin Invest 41: 1887 1962
- Wakkenström, J Acta Med Scand 170: 263 1946

- Jacobs A *Clinical Science and Molecular Medicine* 63 105 1977
- Jasinsky H *Med Wochr* 79 1255 1949
- Jasinsky B *Praxis* 39 811 1950
- Jungner J *Läkartidningen* 63 2602 1966
- Kilpatrick G In Iron deficiency pathogenesis clinical aspects therapy  
Hallberg L Harwerth H -C Vanotti A Eds Academic Press  
London-New York 1970 p 441
- Laholais and Berry 1969 cited from 'Lack of compliance with doctors orders  
A review' *Folia Ciba Geigy* (In Swedish) 1 2 1977
- Layrisse M and Martinez-Torres C In *Progress in ematology* Brown, E  
Moore C V Eds Grune & Stratton New York-London 7 137 1971
- Layrisse M, Martinez-Torres C and Roche M *Am J Clin Nutr* 21 1175  
1968
- Layrisse M Cook, J Martinez-Torres C Roche M Kuhn I and  
Finch C *Blood* 33 430 1969
- Liedén, G *Scand J Haematol* 11 342 1973
- Lindell B Strandberg O and Reizenstein, P *Phys Med Biol* 9 189 1963
- Lundwall O *Acta Med Scand* 189 51 1971
- Mackay H M Dobbs R H and Bingham K *Arch Dis Childh* 20 56 1945
- Malahy 1966 cited from 'Lack of compliance with doctors orders A review'  
*Folia Ciba Geigy* (In Swedish) 1 2 1977
- Magnusson B Sölvell L Arvidsson, B and Sjösten, C *Scand J Haematol*  
14: 337 1975
- Martinez-Torres C and Layrisse M *Am J Clin. Nutr* 24 531 1971
- Martinez-Torres C and Layrisse M *Clinics in Haematol* 2 339 1973
- Moore C V In Occurrence causes and prevention of nutritional anemias, p 92  
1969 Bliz G Ed Swedish nutrition foundation Almqvist & Wiksell Uppsala
- Morrow J Dagg J H and Goldberg A *Scot Med J* 13 78 1968
- Natvig H and Vellar O D *Acta Med Scand* 194 463 1973
- Norrby A *Scand J Haematol Suppl* 20 1974
- Norrby A and Sölvell L *Scand J Haematol Suppl* 20 1974
- Oldfelt C O Liedén, G and Ehn L *Läkartidningen* 65 687 1968
- Olsson, S In *Scand Symp on Iron Deficiency and Iron Treatment, Gothenburg*  
1977 Hallberg L Ed Publ by Hæssle Co Mölndal 1979
- Pritchard J A and Mason, R A *J Amer Med Ass* 190 697 1964



## Chapter II

### Hemoglobin fortification of food

#### Absorption of hemoglobin and non heme iron

##### Abstract

A simplified dose response study showed no significant reduction of absorption when the dose was increased from 0.9 to 4.2 mg hemoglobin iron, where absorption was about 20 per cent, but a significant reduction to 11 per cent when dose was increased from 4.2 to 19 mg hemoglobin iron. Nor was any significant absorption inhibition found when 3.5 mg hemoglobin iron were given together with an oatmeal porridge test meal. In contrast, this meal reduced non-heme ferrous iron absorption from 16.7 to 5.5 per cent.

When given on a fasting stomach, no significant difference was found between absorption of hemoglobin and non-heme iron at 3.5 mg dose levels. Numerically hemoglobin iron was slightly superior.

Meat products expected to facilitate absorption of non-heme iron were also studied either given alone or together with a test meal. Mean absorptions of 3.5-10 mg hemoglobin iron in different meals varied between 14.7 and 18.9 per cent, as compared to mean absorptions of non-heme iron between 5.5 and 7.9 per cent.

In contrast, hemoglobin iron absorption was reduced to only 8 to 7.6 per cent when baked products such as bread or liver-pâté were studied. Even so however mean hemoglobin iron absorptions were 2 to 3 times higher than those of non-heme iron.

The cause of the absorption inhibition in bread was studied. No correlation could be found to the content of bran. No significant inhibition was found when unbaked sour leaven dough was eaten. However when hemoglobin was heated to baking temperature for baking times absorption was reduced as in bread. Hemoglobin breakdown during prolonged heating is thus suggested.

No significant difference was found between hemoglobin capsules and hemoglobin tablets.

The present results suggest that hemoglobin fortification can contribute substantial amounts of absorbed iron. A single meal containing about 5 mg hemoglobin iron seems to provide about 0.8 mg of absorbed iron. This alone corresponds to the total iron requirements of a woman with a loss of 30 ml blood per menstruation.

- Walker, R and Williams R In Iron in Biochemistry and Medicine Academic Press London-New York 1974
- Watkins et al 1967 cited from "Lack of compliance with doctors orders  
A review Folia Ciba Gelvy (in Swedish) 1 2 1977
- Vellar O D In Scand Symp on Iron Deficiency and Iron Treatment, Gothenburg 1977 Hallberg L Ed Publ by Hässle Co Mölndal 1979
- Vellar O and Hermansen L Acta Med Scand : Suppl 522 1971
- Weinfeld A Acta Med Scand Suppl 427 1966
- Widdowson E M Edholm O G and McCance H A Brit. J Nutr 8 147 1954

hemoglobin with non radio-active hemoglobin produced in an similar way

The hemoglobin was administered in gelatin capsules each containing approximately 400 mg hemoglobin. These capsules were taken together with water after an 8 hours fast.

## SUBJECTS

All absorption studies were performed in subjects suspected to have latent iron deficiency i.e. women in the fertile age group (Höglund et al 1970) or male blood donors (Liedén 1974). A total of 186 iron absorption tests were performed in 88 such subjects. Three different dose levels of hemoglobin iron were studied and hemoglobin was administered in 16 different forms or meal combinations.

## Dose response

A simple dose response curve for hemoglobin iron absorption was established in 6 blood donors.

## Heme and non-heme iron absorption

Comparison studies of the absorption of non-heme and heme iron were performed in a total of 64 subjects young females and males where 28 took non-heme iron fasting and in 4 different meal compositions. Absorption of hemoglobin iron was studied in 42 subjects who took it fasting and in 6 different meal compositions.

## Hemoglobin stability during baking

Because it was found that hemoglobin iron is poorly absorbed from bread, different stages of the baking procedure were examined in 2 male blood donors and 1 male volunteer. For the same reason, the iron absorption from hemoglobin denatured in three different steps, was studied in 3 volunteer blood donors.

## Pharmaceutical hemoglobin preparation

In order to study the influence on absorption, the pharmaceutical preparation of hemoglobin absorption was studied in 12 blood donors. They were given three different preparations, fasting or together with a test meal, which had previously been found to inhibit the absorption of non-heme iron appreciably and milk (Höglund et al 1970). Two kinds of tablets containing 20 mg hemoglobin iron were kindly prepared by Astra Pharmaceutical Co, Södertälje, Sweden, one high and one low pressure tablet. The absorption of hemoglobin iron from the softer and the harder tablet was compared to that of hemoglobin in gelatin capsules.

## INTRODUCTION

In 1974 the World Health Organization Regional Office for Africa listed anemia as one of the five most important medical problems in that area and iron deficiency is one of the causes of anemia. Attempts to prevent iron deficiency anemia have included increasing the iron intake either by fortification or by medication, but almost exclusively with the use of non-heme iron. At the present time Sweden seems to have the world's highest level of fortified flour with 6.5 mg iron/100 g flour.

However, the efficacy of fortification with non-heme iron has been questioned (Reizenstein et al 1979) and it has been difficult to demonstrate any correlation between the intake of non-heme iron and the frequency of iron deficiency anemia (Reizenstein et al 1979).

In contrast, iron deficiency seems to be more rare among subjects with a high meat intake and consequently with a high heme iron intake than among subjects getting their iron mostly in the non-heme form (Takkunen 1976). Similarly, iron deficiency appears to be more frequent or at least more widely publicized in countries where the iron is derived mainly from cereals or vegetables such as in East Africa, parts of Asia and Sweden, than in areas with a high meat and heme iron intake, as for instance in the Masai areas of Africa, the USA, Australia, Argentina or Mediterranean Europe. Finally, it is well known that the absorption mechanism for heme iron differs from and is less vulnerable than that for non-heme iron (Reizenstein 1977, Reizenstein et al 1979). Also, cattle hemoglobin is generally a waste product.

Therefore, the present purpose was to study the absorbability and stability of hemoglobin used for iron fortification.

## METHODS OF ABSORPTION MEASUREMENTS AND PREPARATIONS

Intestinal iron absorption was studied with a whole body counter as described previously (Reizenstein et al 1961, Reizenstein 1973). The whole body counter employed was designed to compensate for variations in measuring efficiency caused by the redistribution of radio-iron in the human body during the absorption process (Reizenstein 1973). About 0.3-0.5  $\mu\text{Ci}$   $^{59}\text{Fe}$  was used for a single absorption study.

### Preparation of radio-active hemoglobin

Radio-active hemoglobin was prepared by intravenous or intramuscular injection of 1 to 2.5 mCi  $^{59}\text{Fe}$  ferric citrate (approximate specific activity 1 mCi per mg) to a calf or a sheep. Two to three weeks later the blood from the animals was collected either by sacrificing the animal or by bleeding it. The blood was centrifuged and the red cells freeze dried. The lyophilized powder consisted of 70-80 per cent hemoglobin. The specific activity of the hemoglobin varied between 1 and 5  $\mu\text{Ci}$  per g hemoglobin.

When necessary, this specific activity was reduced by diluting the radio-active he-

In contrast, the absorption decreased statistically significantly ( $p < 0.05$ ) to about 11 per cent when hemoglobin iron dose was increased from 4.2 to 19.3 mg (Table 1)

Table 1 Simplified dose-response curve for hemoglobin iron absorption by fasting, male blood donors

Dose of iron, mg	No. of subjects	Mean absorption	Se of mean
0.85	6	21.5%	4.20
4.2	6	20.3%	4.52
19.3	6	10.8%	2.41

#### COMPARISON OF HEME AND NON HEME IRON ABSORPTION

Under experimental conditions, with the iron given on a fasting stomach, the mean absorption of 3.5 mg iron from ferrous sulphate was not statistically significantly different from that of hemoglobin in subjects with latent iron deficiency (Tables 2-3). However, although the ferrous sulphate was administered in solution, in contrast to the hemoglobin, which was administered in capsules, the numerical absorption of 3.5 and 4.2 mg hemoglobin iron was slightly higher (18.8 and 20.3 per cent, Tables 1 and 3) than that of 3.5 mg ferrous sulphate iron (16.7 per cent, Table 2).

Table 2 Comparison studies of the absorption of non-heme, ferrous sulphate iron

Type of test	Subjects	Number	Absorption Mean $\pm$ S.E.M.
3.5 mg iron fasting	Young females	8	16.7 $\pm$ 4.4
3.5 mg iron test meal	Young females	6	5.5 $\pm$ 2.3
1 mg iron in sausage test meal	Young females	8	7.9 $\pm$ 2.3
10 mg iron in dark bread	Apparently healthy male volunteers	8	0.9 $\pm$ 0.42
10 mg iron in dark bread with extra bran	Apparently healthy male volunteers	8	0.8 $\pm$ 0.25

At a realistic fortification level, between 3.5 and 10 mg (iron per meal) and when the iron was administered in the form of a fortified sausage together with a test

The iron absorption from a sausage containing 5 mg non-heme iron and 16.5 mg hemoglobin iron per 100 g was studied. It was given together with the test meal described above. Each person ate 20 g sausage corresponding to 9 mg non-heme iron and 3.5 mg heme iron. Hamburgers and baked liver-pâté were prepared containing 10 mg hemoglobin per portion.

### Hemoglobin in bread

Three different kinds of bread were fortified with ferrous iron or hemoglobin. White sifted wheat flour bread, brown whole meal rye bread and brown whole meal bread with extra bran added were used. Two hemoglobin fortification levels were used: one with 1 mg iron per portion, the other with 10 mg iron.

Unbaked wheat and whole meal dough, used for white and brown bread respectively, was given to 3 volunteers. The amount of heme iron per portion was the same as that given in the finished bread. Since the hemoglobin used to fortify bread is subjected to a pH about 4 at 90 °C for 60 minutes during the baking, hemoglobin similarly treated was fed to the same 3 volunteers in order to study the absorption of iron from denatured hemoglobin.

The denaturation of hemoglobin was performed by heating to 110 °C for 1 minute at pH 7.

### Bleached hemoglobin - a protein extender

A bleached hemoglobin product is being produced in Sweden, to be used as a protein extender. To study the iron absorption from this product, bleached in the laboratories of Elco Protein with  $H_2O_2$  and HCl, amounts containing 3.5 mg iron were given to test persons as well as meat ball portions containing 3.5 mg iron derived from bleached hemoglobin.

The preparation of the 15 different foods or food components fortified with ferrous iron or native or bleached hemoglobin was performed by Mrs Birgit Slesby, Department of Meat Technology, Royal Agricultural School, Copenhagen, Denmark, by Mr Agne Bergkvist, Swedish Meat Research Institute, Kivlinge, Sweden, by Mr I. Forslund, Schulstad Bakery, Copenhagen, Denmark, by Kungälvsmen Bakery, Södertälje, Sweden, and by Globe Foods, Stockholm, Sweden. Their co-operation is gratefully acknowledged.

## RESULTS

### Response of absorption to hemoglobin dose

No statistically significant decrease in absorption was found when the hemoglobin dose was increased from 0.85 to 4.2 mg hemoglobin iron per meal (Table 1); the absorption remained about 20 per cent.

In contrast, the absorption decreased statistically significantly ( $p < 0.05$ ) to about 11 per cent when hemoglobin iron dose was increased from 4.2 to 19.3 mg (Table 1)

Table 1 Simplified dose-response curve for hemoglobin iron absorption by fasting, male blood donors

Dose of iron, mg	No of subjects	Mean absorption	Se of mean
0.85	6	21.5 %	4.20
4.2	5	20.3 %	4.52
19.3	5	10.8 %	2.41

#### COMPARISON OF HEME AND NON-HEME IRON ABSORPTION

Under experimental conditions with the iron given on a fasting stomach, the mean absorption of 3.5 mg iron from ferrous sulphate was not statistically significantly different from that of hemoglobin in subjects with latent iron deficiency (Tables 2-3). However, although the ferrous sulphate was administered in solution, in contrast to the hemoglobin, which was administered in capsules, the numerical absorption of 3.5 and 4.2 mg hemoglobin iron was slightly higher (18.8 and 20.3 per cent, Tables 1 and 3) than that of 3.5 mg ferrous sulphate iron (16.7 per cent, Table 2).

Table 2 Comparison studies of the absorption of non-heme, ferrous sulphate iron.

Type of test	Subjects	Number	Absorption Mean $\pm$ S.E.M.
3.5 mg iron - fasting	Young females	8	18.7 $\pm$ 4.4
3.5 mg iron test meal	Young females	6	5.5 $\pm$ 2.3
1 mg iron in sausage test meal	Young females	8	7.9 $\pm$ 2.3
10 mg iron in dark bread	Apparently healthy male volunteers	8	0.8 $\pm$ 0.42
10 mg iron in dark bread with extra bran	Apparently healthy male volunteers	8	0.8 $\pm$ 0.25

At a realistic fortification level between 3.5 and 10 mg iron per meal and when the iron was administered in the form of a fortified sausage together with a test

meal the absorption of hemoglobin iron (17.8 per cent, Table 3) was twice as high as that of ferrous sulphate (7.8 per cent, Table 2). This difference was statistically significant ( $p < 0.001$ ). In spite of the expected absorption promotion of non-heme iron by the meat in the sausage. In fact the hemoglobin iron absorption percentages from up to 10 mg iron in all non-baked foods or food components (Tables 3 and 4) seem to supply 1.5 - 1.8 mg absorbed iron per fortified portion.

### Hemoglobin iron absorption from bread

The absorption was 4 to 10 times lower from bread (1.5 to 3.8 per cent) than from sausage or hamburger (Table 3). The absorption inhibition seemed unrelated to the bread content of iron absorption inhibitors known to be present in bran (Table 3). Thus absorption was as low from white bread as from whole meal bread (Table 3). Similarly when the phytic acid content of bread was artificially increased by the addition of bran, no significant inhibition of hemoglobin iron absorption could be found (Table 3).

Table 3 Absorption of hemoglobin iron

Meal composition	Subjects	No of subjects	Absorption Mean $\pm$ S.E.M
3.5 mg hemoglobin iron in capsules-fasting	Young male blood donors	14	18.8 $\pm$ 3.3
3.5 mg hemoglobin iron in sausage + test meal	Young female and male blood donors	14	17.8 $\pm$ 1.45
10 mg hemoglobin iron in hamburger	Young male and female blood donors	8	14.7 $\pm$ 6.11
10 mg hemoglobin iron in baked liver-pâté	Young male and female blood donors	8	7.6 $\pm$ 5.34
1 mg hemoglobin iron in baked white bread	Young male and female blood donors	6	1.5 $\pm$ 0.72
10 mg hemoglobin iron in baked brown bread	Apparently healthy male volunteers and blood donors	8	3.8 $\pm$ 1.59
1 mg hemoglobin iron in baked brown bread	- " -	6	1.6 $\pm$ 1.28
10 mg hemoglobin iron in brown bread baked with extra bran	- " -	8	2.8 $\pm$ 0.53

At the 10 mg iron level the absorption of hemoglobin from brown bread was lower (2.8-3.8%, Table 3) than that from meat, but the absorption of ferrous iron was even worse (0.8-0.9%, Table 2).



Less iron was absorbed from dark bread at the 10 mg level from ferrous iron (about 0.8 per cent) than from hemoglobin used for the fortification of bread (2.8 to 3.8 per cent Tables 2 and 3) but this difference was not significant statistically

Table 4 Iron absorption from 1 mg iron in hemoglobin at different stages of the baking process, and from bleached hemoglobin

Form and conditions of administration	Material	No of subjects	Absorption, mean % $\pm$ S.E. of mean
<u>Baking</u>			
Wheat dough (pH 6) fasting subjects	Hemoglobin in dough	2 blood donors + 1 male volunteer	18.9 $\pm$ 14.61
Dark sour dough (pH 4) prior to baking fasting subjects		2 blood donors + 1 male volunteer	12.6 $\pm$ 9.88
Hemoglobin, heated to 90 C at pH 4 for 60 minutes fasting subjects	Heated hemoglobin	2 blood donors + 1 male volunteer	4.5 $\pm$ 0.75
<u>Bleached hemoglobin</u>			
Capsulated; fasting subjects	Denatured bleached hemoglobin	3 blood donors	5.4 $\pm$ 0.85
Capsulated, with test meal	Denatured bleached hemoglobin	3 blood donors	0.3 $\pm$ 0.57
In fortified meat balls	Denatured bleached hemoglobin	3 blood donors	1.7 $\pm$ 3.0
<u>Comparison</u>			
Capsulated; fasting subjects	Native hemoglobin	2 blood donors + 1 male volunteer	14.1 $\pm$ 3.93

meal the absorption of hemoglobin iron (17.8 per cent Table 3) was twice as high as that of ferrous sulphate (7.9 per cent Table 2). This difference was statistically significant ( $p < 0.001$ ) in spite of the expected absorption promotion of non heme iron by the meat in the sausage. In fact the hemoglobin iron absorption percentages from up to 10 mg iron in all non-baked foods or food components (Tables 3 and 4) seem to supply 1.5 - 1.8 mg absorbed iron per fortified portion.

### *Hemoglobin iron absorption from bread*

The absorption was 4 to 10 times lower from bread (1.5 to 3.8 per cent) than from sausage or hamburger (Table 3). The absorption inhibition seemed unrelated to the bread content of iron absorption inhibitors known to be present in bran (Table 3). Thus absorption was as low from white bread as from whole meal bread (Table 3). Similarly when the phytic acid content of bread was artificially increased by the addition of bran no significant inhibition of hemoglobin iron absorption could be found (Table 3).

Table 3 Absorption of hemoglobin iron

Meal composition	Subjects	No of subjects	Absorption Mean $\pm$ S.E.M
3.5 mg hemoglobin iron in capsules-fasting	Young male blood donors	14	18.8 $\pm$ 3.3
3.5 mg hemoglobin iron in sausage + test meal	Young female and male blood donors	14	17.8 $\pm$ 1.45
10 mg hemoglobin iron in hamburger	Young male and female blood donors	8	14.7 $\pm$ 6.11
10 mg hemoglobin iron in baked liver-pâté	Young male and female blood donors	8	7.6 $\pm$ 5.34
1 mg hemoglobin iron in baked white bread	Young male and female blood donors	6	1.5 $\pm$ 0.72
10 mg hemoglobin iron in baked brown bread	Apparently healthy male volunteers and blood donors	8	3.8 $\pm$ 1.59
1 mg hemoglobin iron in baked brown bread	- -	6	1.6 $\pm$ 1.28
10 mg hemoglobin iron in brown bread baked with extra bran	- -	8	2.8 $\pm$ 0.63

At the 10 mg iron level the absorption of hemoglobin from brown bread was lower (2.8-3.8% Table 3) than that from meat but the absorption of ferrous iron was even worse (0.8-0.9% Table 2).

Table 5 Effect, on hemoglobin iron absorption, of the pressure used when preparing hemoglobin tablets, or encapsulation of hemoglobin.  
(Fasting blood donors given 20 mg hemoglobin iron.)

Form of preparation	No of subjects	Absorption Mean $\pm$ S.E. of mean, in per cent
Low pressure tablet	6	10.0 $\pm$ 2.78
High pressure tablet	5	9.3 $\pm$ 3.63
Gelatin capsule	8	9.0 $\pm$ 3.12

If hemoglobin fortification would result in an approximate intake of 3.5 mg hemoglobin iron per main meal or 7 mg of hemoglobin iron per day an average iron absorption of approximately 1 mg per day would be achieved from this alone. This is appreciably more than the calculated absorption from the iron presently used for the fortification of flour (Björklund et al 1970, Heizenstein et al 1979).

Prevention of iron deficiency can take the form of food fortification or of food supplements. Hemoglobin iron appears to be suitable mainly for the prevention, not for the treatment of iron deficiency since its iron content is low. Hemoglobin administration will result in iron intakes at a therapeutic level only if exceptional methods are used such as giving large amounts of hemoglobin granulates on food. It is true that isolated heme has a higher iron content than hemoglobin, but unless the heme molecule is changed, absorption will be unsatisfactory.

However, even if special methods could be used to administer larger amounts of hemoglobin or heme iron, the present studies show that one would rapidly approach a point of diminishing returns. There is a sharp drop in the absorption at absorption levels somewhere between 4.3 and 10.3 mg.

Since cereals generally contain iron absorption inhibitors, it was hoped that hemoglobin iron fortification of cereal products could replace to some extent, the conventional fortification with non-heme, metallic so-called reduced iron. However the present results suggest a hemoglobin breakdown during the prolonged heating when bread is baked. The low pH in sour dough seems less harmful. This break-down may also explain the relatively low absorption of hemoglobin iron used for the fortification of liver-país which is also baked, although at lower temperatures and for shorter times (60 C 45 minutes).

In spite of the heme break-down, the absorption of the remaining intact hemoglobin iron from bread results in significantly higher uptake than ferrous sulphate fortification. There are reasons to assume that heme iron absorption is even more superior to that of the conventionally used metallic iron (Björklund et al 1970, Björn Rasmussen et al 1977).

## Hemoglobin stability during baking

Since the low absorption in bread seemed unrelated to the bran content, the effect of temperature and pH during baking was examined. The absorption was statistically significantly inhibited neither in unbaked cold wheat dough nor in unbaked sour dough (Table 4). In contrast when hemoglobin was heated to 90°C at pH 4 for 80 min at a pH and temperature corresponding to those used during baking, a statistically significant ( $p < 0.05$ ) decrease in the mean absorptions was found (Table 4).

## Hemoglobin iron absorption from meat products

Statistically significantly ( $p < 0.05$ ) more iron was absorbed from hemoglobin used to fortify (non-baked) hamburgers or meat sausage than from that used to fortify baked liver-pâté (Table 3). Heat denaturation during baking of the pâté is believed to explain this difference. The absorption from 10 mg hemoglobin iron in hamburgers was not statistically significantly lower than that of 3.5 mg hemoglobin iron given on a fasting stomach (Table 3).

## Iron absorption from bleached hemoglobin

Hemoglobin is bleached by the food industry in order to obtain a protein powder without the heme colour to be used as a replacement protein. Even when this powder was given on a fasting stomach and despite the use of a dose of only 1 mg iron, the percentage absorption was statistically significantly lower from the protein powder than from native hemoglobin (Table 4). Moreover when this denatured hemoglobin powder was given together with a test meal, a statistically significant ( $p < 0.01$ ) inhibition of the iron absorption was found. This was true for two different test meals (Table 4) and suggests that the iron in the bleached hemoglobin is partially or largely non-heme iron.

## EFFECT OF THE PHARMACEUTICAL HEMOGLOBIN PREPARATION

No statistically significant difference could be found between the absorption of labelled hemoglobin iron given in the form of a capsulated powder, a soft low-pressure tablet and a hard high pressure tablet (Table 5).

## CONCLUSIONS

The use of hemoglobin iron for the fortification of meat products seems to result in satisfactory iron absorption. No evidence was found in the present study of any inhibition of the iron absorption by cereals eaten together with the hemoglobin iron. It is reasonable to assume that even if non-heme iron was used for the fortification of meat products which enhance its absorption rather than for that of bread which inhibits it, it would still be much less well absorbed than hemoglobin iron (Tables 2 and 3). This seems to be true even when ferrous sulphate is used as the non-heme iron. The reduced metallic iron normally used for fortification purpose in Sweden is usually even less well absorbed than ferrous sulfate (Höglund et al 1970).

Table 5 Effect, on hemoglobin iron absorption, of the pressure used when preparing hemoglobin tablets, or encapsulation of hemoglobin.  
(Fasting blood donors given 20 mg hemoglobin iron.)

Form of preparation	No of subjects	Absorption, Mean $\pm$ S.E. of mean, in per cent
Low pressure tablet	6	10.0 $\pm$ 2.73
High pressure tablet	6	8.3 $\pm$ 2.63
Gelatin capsule	8	9.0 $\pm$ 2.12

If hemoglobin fortification would result in an approximate intake of 3-7 mg hemoglobin iron per main meal, or 7 mg of hemoglobin iron per day, an average iron absorption of approximately 1 mg per day would be achieved from this alone. This is appreciably more than the calculated absorption from the iron presently used for the fortification of flour (Höglund et al 1970, Reizenstein et al 1979).

Prevention of iron deficiency can take the form of food fortification or of food supplements. Hemoglobin iron appears to be suitable mainly for the prevention, not for the treatment of iron deficiency, since its iron content is low. Hemoglobin administration will result in iron intakes at a therapeutic level only if exceptional methods are used, such as giving large amounts of hemoglobin granulates on food. It is true that isolated heme has a higher iron content than hemoglobin, but unless the heme molecule is changed, absorption will be unsatisfactory.

However, even if special methods could be used to administer larger amounts of hemoglobin or heme iron, the present studies show that one would rapidly approach a point of diminishing returns. There is a sharp drop in the absorption at absorption levels somewhere between 4.3 and 19.3 mg.

Since cereals generally contain iron absorption inhibitors, it was hoped that hemoglobin iron fortification of cereal products could replace, to some extent, the conventional fortification with non-heme, metallic, so-called reduced iron. However, the present results suggest a hemoglobin breakdown during the prolonged heating when bread is baked. The low pH in sour dough seems less harmful. This breakdown may also explain the relatively low absorption of hemoglobin iron used for the fortification of liver-pâté, which is also baked, although at lower temperatures and for shorter times (50°C, 45 minutes).

In spite of the heme break-down, the absorption of the remaining intact hemoglobin iron from bread results in significantly higher uptake than ferrous sulphate fortification. There are reasons to assume that heme iron absorption is even more superior to that of the conventionally used metallic iron (Höglund et al 1970, Björn-Rasmussen et al 1977).

## Hemoglobin stability during baking

Since the low absorption in bread seemed unrelated to the bran content the effect of temperature and pH during baking was examined. The absorption was statistically significantly inhibited neither in unbaked cold wheat dough nor in unbaked sour dough (Table 4). In contrast, when hemoglobin was heated to 90°C at pH 4 for 60 min a pH and temperature corresponding to those used during baking a statistically significant ( $p < 0.05$ ) decrease in the mean absorptions was found (Table 4).

## Hemoglobin iron absorption from meat products

Statistically significantly ( $p < 0.05$ ) more iron was absorbed from hemoglobin used to fortify (non-baked) hamburgers or meat sausage than from that used to fortify baked liver-pâté (Table 3). Heat denaturation during baking of the pâté is believed to explain this difference. The absorption from 10 mg hemoglobin iron in hamburgers was not statistically significantly lower than that of 3.5 mg hemoglobin iron given on a fasting stomach (Table 3).

## Iron absorption from bleached hemoglobin

Hemoglobin is bleached by the food industry in order to obtain a protein powder without the heme colour to be used as a replacement protein. Even when this powder was given on a fasting stomach and despite the use of a dose of only 1 mg iron the percentage absorption was statistically significantly lower from the protein powder than from native hemoglobin (Table 4). Moreover when this denatured hemoglobin powder was given together with a test meal a statistically significant ( $p < 0.01$ ) inhibition of the iron absorption was found. This was true for two different test meals (Table 4) and suggests that the iron in the bleached hemoglobin is partially or largely non-heme iron.

## EFFECT OF THE PHARMACEUTICAL HEMOGLOBIN PREPARATION

No statistically significant difference could be found between the absorption of labelled hemoglobin iron given in the form of a capsulated powder, a soft low-pressure tablet and a hard high pressure tablet (Table 5).

## CONCLUSIONS

The use of hemoglobin iron for the fortification of meat products seems to result in satisfactory iron absorption. No evidence was found in the present study of any inhibition of the iron absorption by cereals eaten together with the hemoglobin iron. It is reasonable to assume that, even if non-heme iron was used for the fortification of meat products which enhance its absorption, rather than for that of bread which inhibits it, it would still be much less well absorbed than hemoglobin iron (Tables 2 and 3). This seems to be true even when ferrous sulphate is used as the non-heme iron. The reduced metallic iron normally used for fortification purposes in Sweden is usually even less well absorbed than ferrous sulfate (Höglund et al 1970).

## Abstract

There are 4 reasons to examine heme iron absorption

- 1 Vegetable diets and iron deficiency anemia in developing countries
- 2 difficulties to refill iron stores in women in industrialized countries
- 3 non-use of cattle hemoglobin for human nutrition and
- 4 differences in absorption between heme and non-heme iron. Twenty-eight different preparations and combinations of  $^{59}\text{Fe}$ -heme were fed to 84 volunteers with latent iron deficiency

Four methods to prepare heme were tested. UV-spectrophotometry used to examine the degree of heme polymerization showed unprecise spectra for heme prepared with acetic acid acetone which suggests polymerization. About 40 mg histidine/mg heme sharpened spectra probably since dihistidine-heme monomers were formed.

Calculations described earlier indicate that the net absorption increases when the diet is supplemented with 20 mg ferrous iron daily and when the iron is given with meals. It is only 0.8 mg/day. In contrast, it has been calculated that if 20 mg hemoglobin iron are given it is 2.2 mg/day. If 20 mg heme iron in ordinary or enteric-coated capsules was given alone or together with buffering substances absorption was unsatisfactory (about 0.15 mg iron).

It was also unsatisfactory (about 0.4 mg) from solutions containing glycine or histidine. However satisfactory absorptions (about 2 mg) were obtained from a buffered pH 8 water solution of hemin containing nicotinic acid and of an oil solution of hemin-di-methyl ester.

## INTRODUCTION

Iron deficiency anemia is a common disease in developing countries for a number of reasons outlined earlier (for references see Reizenstein 1974). Iron intake in several developing countries is appreciably higher than it is in industrialized countries, but in many areas consists of almost exclusively non-heme iron, the intestinal absorption of which is inhibited by largely vegetable diets.

In industrialized countries, iron deficiency anemia is becoming relatively rare. However latent iron deficiency (i.e. depleted iron stores) is still common (for references see Hallberg et al 1970, Klaf 1975). The reason appears to be that absorption of the largely non-heme therapeutic or supplemental iron is strongly stimulated as long as there is anemia, but that absorption decreases sharply when the hemoglobin concentration approaches normal. The stimulation during the

# REFERENCES

- Björn-Rasmussen E Hallberg L and Rossander L Br J Nutr 37 375  
1977
- Höglund S Blood 34 505 1969
- Höglund S Ehn L and Liedén, G Acta Haemat 44 193 1970
- Liedén, G Linköping University Medical Dissertations No 22 1974
- Reizenstein P Clinical whole body counting Publ by John Wright & Sons  
Bristol 1973
- Reizenstein P Sw Pharmaceutical J (Svensk Farmaceutisk Tidskrift, in  
Swedish) 81,385 1977
- Reizenstein P Carlmark, E Ehn, L and Stenby B In Scand Symp  
on Iron Deficiency and Iron Treatment, Gothenburg 1977 L Hallberg  
Ed Publ by Hässel Co Mölndal 1979 p 25
- Reizenstein P Price D C Cronkite E P Cohn, S H and Wasserman,  
L Trans Eur Soc Hematol 8 237 1961
- Takdaman, H J Haematol Suppl 125 1 1976



- 4 Acetic acid extraction (Labbe et al 1967 Falk 1967) was found to be the most suitable method

## Characterization of porphyrin

Attempts were made to examine with u.v. spectrophotometry the aggregation and polymerization condition of the porphyrins isolated

## Hemin iron preparations

Customary procedures were used when solubilizing compounds (NaOH  $\text{Na}_2\text{CO}_3$  and the basic amino-acid arginine) and co-ordinating compounds like nicotinic acid (tab 1) nicotinamide xylitol pentanlootinate and histidine were added (tab 1) Buffers sometimes containing ascorbic acid or glycine were used in some experiments (tab 1) An attempt was made to prevent polymerization of hemin molecules, previously attributed to bridges between propionic acid side chains on the porphyrin ring by derivatisation of this group to methyl ester (Falk 1967) Enteric coating of some preparations was performed by customary methods

Iron absorption measurements were performed as previously described with a whole body counter (Reisenstein et al 1961)

## RESULTS

### Absorption of hemoglobin iron

Five subjects with latent iron deficiency absorbed an average of 2.2 mg of 20 mg hemoglobin iron given in capsules with or without food Administration prolonged for 7 days did not appear to reduce absorption Comparison values for non-heme iron (0.8 mg) are given in the discussion below

### Characterization of porphyrin

Hemin ( $\text{Fe}^{+++}$ ) dissolved in a  $\text{NaHCO}_3/\text{Na}_2\text{CO}_3$  buffer at pH 11 was found to give ill-defined uv-spectrophotometric peaks in the maxima 380-390 485-500 520-540 (shoulder) and 610-620  $\mu$  region even after acidification or the addition of pyridine as a co-ordinating ligand On the other hand heme ( $\text{Fe}^{++}$ ) obtained by reducing hemin solutions with sodium dithionite gave 4 sharp absorption bands in the u.v. spectrum at 416 480 524 540 (min.) and 558  $\mu$ , after the adding of pyridine When histidine was added to a  $10^{-2}$  -  $10^{-4}$  M heme solution, this resulted in a sharper spectrum than that found in heme alone None of the other amino acids tested had a similar effect

### Absorption of hemin from ordinary capsules

When hemin was encapsulated alone or together with sodium bicarbonate only an

anemic phase seems to overcome the inhibition of iron absorption effected by food and a prolonged high iron concentration in the intestine. During the phase of latent iron deficiency these effects dominate and they together with the so-called 'marginal tax effect' (Reizenstein et al 1975 d) caused by the shape of the dose-response curve explain why the net increase in iron retention during iron therapy is so small that stores become repleted exceedingly slowly.

Hemoglobin iron is absorbed no better than non-heme iron under experimental conditions i.e. in single doses on a fasting stomach. However its absorption seems to be less inhibited by food and heme does not increase the concentration of ionic iron in the intestine. During realistic nutritional or therapeutic conditions it might therefore have some advantages (Reizenstein et al 1975 a och d). There are in fact some observations indicating that meat-eating populations have less iron deficiency than those eating vegetable diets (Reimann et al 1970, Takken 1976).

Only about 10 % of the hemoglobin produced by Swedish slaughterhouses is used for human consumption (Reizenstein 1975 a och b). In countries with productions much higher than Sweden the percentage is probably smaller.

Thus large quantities of heme iron as well as of globin are available as sources of possible valuable dietary supplemental or therapeutic iron.

These are the four main reasons for the present study of the solubility and absorbability of heme and of its state of aggregation.

## Materials

Radio-active hemoglobin was prepared by injecting  $750 \mu\text{Ci}^{59}\text{FeCl}_3$  intravenously to calves being sacrificed 2 weeks later. From their carotid arteries approximately 4 l blood was obtained and collected in sterile 1 litre bottles containing 80 ml 0.2 % sodium citrate. Bottles were flown or transported to an Ecal Food Drier (E. Carlsson, Munka-Ljungby) and blood was dried at 70 °C. Radio-iron absorption was studied in 84 volunteer blood donors with latent iron deficiency.

## METHODS OF SEPARATING HEME AND GLOBIN OF CHARACTERIZING PORPHYRINS AND OF PREPARING HEME IRON

### Separation of heme, hemin or hematin from globin

The following methods were tested:

1. Trypsin digestion (Conrad et al 1967 a och b) with and without pre-denaturation (100 °C 10 min) was not used because only 32 per cent of protein was recovered in lyophilized dialysates.
2. Glacial acetic acid (Fischer 1941) precipitation followed by dialysis against 0.9 per cent NaCl was not used since it resulted in unsatisfactory recovery of crude hemin precipitates.
3. Methyl-ethyl-ketone extraction (Yonetani 1967, Teale 1959) was not used despite 75 per cent protein recoveries because of high solvent requirements.

It appears probable both when considering hemoglobin iron absorption and in regard to the present results that monomeric non-aggregated soluble heme would be absorbable. The problem is that the solubility qualities of heme are complicated and that it forms polymers and aggregates easily.

Heme has two carboxylic acid or propionamide and two vinyl side chains. It is partly lipid soluble and partly water soluble. The reason for this is probably the arrangement with the lipophilic vinyl side chains of heme fixed in a hydrophobic pocket (Antonini 1971) in the globin molecule while the hydrophilic propionamide side chains are sticking out into the mainly aqueous biological environment.

Esterification of the carboxylic acid side chains increases the solubility in organic solvents (Falk 1967). If the polar side chains could be removed like in aetioporphyria which has only vinyl side chains, solubility in lipid solvents would increase (Falk 1967). Similarly if all vinyl side chains could be removed or replaced heme would become entirely water soluble. These facts explain why heme is poorly soluble and absorbable although it resembles compounds such as vitamin B<sub>12</sub>, uroporphyrin I and coproporphyrin I and II, which are more easily soluble.

These considerations also explain why better absorption was obtained when heme was solubilized either in oil by esterification of the polar side chains or in water by alkalization with sodium carbonate or sodium hydroxide. However solubilization of heme is not enough to obtain optimal absorption; polymerization and dimerization must also be prevented (Antonini 1971). Polymerization may take place via OH- links between the iron atoms. Both heme and hemin in water are at least dimeric (Ehrenberg 1957) and the free iron co-ordination sites are occupied by water or hydroxyl ions, depending on pH.

Polymerization is difficult to avoid since experiments usually have to be performed in alkaline solutions (Falk 1967). Polymerization is less pronounced in ferri-coproporphyrin, which has 4 propionate acid polar side chains and thus a large electrostatic field, or ethanol (Falk 1967). Since it is thought that sharp bands indicate the formation, by pyridine, of the monomeric bispyridyl complex from the original dimeric bisquo-heme complex or (in neutral solution) from large ionic micelles (Ehrenberg 1957, Kallin 1955) u v spectrophotometry was used to characterize porphyrins in the preparations tested.

Histidine forms one of the ligands between the globin molecule and the iron in hemoglobin (Antonini 1971); these ligands seem to have a special function compared to the 10 other amino acids within van der Waals constant distance of the porphyrin (Antonini 1971).

For this probable reason the addition of histidine was found, at high concentrations to sharpen the heme spectrum by preventing dimerization. This effect however could not be used in practice for two reasons. First, a large amount of histidine was found to be required per molecule of heme (approximately 40 mg/g heme). This is in agreement with Ehrenbergs (1957) finding that in 14 M histidine solutions are required to form heme-di-histidine. Secondly single amino acids at neutral pH are zwitterions and poly-amino-acids would probably offer a better chance to prevent polymerization (Lernberg 1961, Baner et al 1963).

average of 0.14 mg was absorbed (experiments 1, 13, and 22 in Table I) from 20 mg heme iron.

### Absorption of heme in enteric coated capsules

Of 20 mg heme iron encapsulated alone or together with histidine, arginine, sodium carbonate, nicotinic acid, only an average of 0.16 mg was absorbed (experiments 2, 4, 7, 8, 14, 23 in Table I).

### Absorption of heme in solutions

The absorption was poor (0.4 mg of 20 mg heme iron) when a solution of heme in glycine and NaOH was given. When histidine, xylitol pentanicotinate or ascorbic acid were added, no appreciable improvement was noted (experiments 11, 12, 10, 15, 16, 17, 18, 19, 20a, 20b, 27).

The absorption was satisfactory of 20 mg heme iron dissolved at pH 8.0 with addition of histidine (2 mg/mg heme), sodium carbonate (1.65 mg/mg), nicotinic acid (0.8 mg/mg) and ascorbic acid (2 mg/mg). An average of 3 mg was absorbed (experiment 10). The absorption was also satisfactory of heme methyl di-ester dissolved in arachid oil. An average of 2 mg was absorbed (experiments 20 II and 28).

However, the absorption from the water solution sank to 1.4 mg when nicotinic acid was exchanged for nicotinamide and to 0.84 mg when arginine replaced sodium carbonate and nicotinic acid. It also sank, to 0.48 mg, when the doses were reduced of histidine (to 0.4 mg/mg), nicotinic acid (to 0.18 mg/mg) and of ascorbic acid (to 0.4 mg/mg in experiments 5, 8, 9, 10). The absorption from the oil sank to about 0.4 mg when the ester was suspended in oil rather than dissolved or when it was given in capsules.

## DISCUSSION

### Comparison values for the absorption of non-heme iron

Earlier studies (Reizenstein et al 1975a and b) showed that subjects with latent iron deficiency absorbed on an average 4 mg iron of a single 20 mg iron dose in the form of  $\text{FeSO}_4$  given on a fasting stomach and 2.2 mg when the iron was given with food. When continuous daily doses were given on a fasting stomach, 2.8 mg were absorbed from each dose.

Assuming a daily food iron intake of 20 mg, the daily addition of 20 mg iron as  $\text{FeSO}_4$  taken with food was calculated to increase the total absorption of iron by only 0.8 mg/day.

Since 2.2 mg were absorbed from 20 mg hemoglobin iron, and since this seems not to be inhibited by food, it could be assumed that persons with a 20 mg food iron intake would increase their net absorption by 2.2 mg per day if 20 mg hemoglobin iron was added daily or 2-3 times the amount found for non-heme iron.

Tabl I. *In situ* absorption, by apparently healthy blood donors, of iron after administration of 20 mg hem iron in 29 diff rent forms or compositions

Experiment No	Iron preparations	Rationale	No of Subjects	% Absorbed
1	Hemin 250 mg in ordinary capsules	Therapeutic dose given as ordinary capsule to test absorption of hemin iron in the absence of amino acids	7	< 1
2	Hemin 250 mg in enteric coated capsules	Therapeutic dose given as an enteric coated capsule with capsule disintegration to start at pH 5-6 This study was meant to avoid exposing the hemin to the acid conditions of the stomach	7	< 1
3	Hemin 45 mg in ordinary capsules	Tracer dose to assess whether dose size of hemin influenced the absorption of hemin iron	6	< 1
4	Hemin 45 mg in enteric coated capsules	As study 3 but given as enteric coated capsules	6	3.7
5	20 ml solution pH 8 containing Hemin 250 mg Arginine 500 mg Histidine 500 mg Ascorbic Acid 450 mg	Hemin dissolved in a solution containing histidine which was reported as successful in improving the absorption of iron from hemoglobin. Arginine was the only basic amino acid in solution that would dissolve hemin. Ascorbic acid was incorporated to maintain the pH at 8	4	4.2 ± 1.6

In conclusion heme iron is well absorbed from hemoglobin where the globin keeps heme soluble and prevents polymerization. When globin is split off heme solubility becomes a problem and at the pH where it is soluble hydroxide bridges between iron cause at least dimerization and probably polymerization.

Heme is soluble in alkali but this solubility could probably be increased if the vinyl side chains could be replaced. It can also be made soluble in oil if the polar carboxylic acid side chains are esterified but some polymerization of the ester seems to occur.

Polymerization can be prevented by forming heme - dihistidine but this requires unpractically large quantities of histidine. It appears probable that absorbable monomeric soluble heme will be obtained only when the free ligands of iron have been blocked and when simultaneously heme has either been made water soluble by modification of the vinyl side chains or lipid soluble by the modification of the polar side chains.

Experiment No	Iron preparations	Italcin®	No of Subjects	% Absorbed
10	<p>20 ml solution pil 8 containing</p> <p> Hemlin 250 mg  Nicotinic Acid 500 mg  Sodium Carbonate 200 mg  Ascorbic Acid 500 mg  Sodium Carbonate 400 mg </p>	Nicotinamide was substituted for nicotinic acid as the latter resulted in considerable subject discomfort due to its vasodilatory properties	4	72 ± 13
13	<p> Hemlin 250 mg  Nicotinic Acid 200 mg  Sodium Carbonate 150 mg  Ilietidine 100 mg  Ascorbic Acid 100 mg </p> <p>In ordinary capsules</p>	Preparation 8 given in ordinary capsule form	4	31 ± 21
14	<p> Hemlin 250 mg  Nicotinic Acid 200 mg  Sodium Carbonate 150 mg  Ilietidine 100 mg  Ascorbic Acid 100 mg </p> <p>In enteric coated capsules</p>	Preparation 9 given in enteric coated capsule form to protect from the stomach acid content	4	0
15	<p> Hemlin 250 mg  Glycine 500 mg  Sodium Hydroxide 40 mg </p> <p>In 10 ml of water pil 8</p>	The amino acids in the above preparations may not have sufficient buffering capacity to overcome the stomach acids. Hemlin was therefore dissolved in a high capacity glycine buffer for absorption studies	4	20 ± 14

Experiment No	Iron preparations	Rationale	No of Subjects	% Absorbed
6	20 ml solution pH 8 containing Hemin 250 mg Sodium carbonate 400 mg Histidine 500 mg Nicotinic Acid 200 mg Ascorbic Acid 500 mg	Hemin in solution containing histidine and ascorbic acid for the reasons stated above Sodium carbonate inorganic base to promote solubilization of hemin Nicotinic acid reported to promote absorption of small quantities of hemin when given in large excess	4	$14.9 \pm 2.9$
7	Hemin 250 mg Histidine 250 mg Arginine 250 mg In enteric coated capsules	Preparation similar to 5 but presented as an enteric coated capsule to protect the ingredients against the acid contents of the stomach. On dialysis of the capsule at pH 5.6 the arginine should assist in solubilizing hemin	4	$0.2 \pm 0.3$
8	Hemin 250 mg Histidine 250 mg Sodium Carbonate 250 mg In enteric coated capsules	As 7 but with sodium carbonate added as the base	3	$1.0 \pm 0.5$
9	Hemin 250 mg Sodium Carbonate 100 mg Histidine 100 mg Nicotinic Acid 45 mg Ascorbic Acid 100 mg In 20 ml solution pH 8	The same ingredients as 6 Reduced amounts of amino acids to see whether the high absorption recorded for 6 was dependent upon the molar concentration of the amino acid	4	$2.3 \pm 0.3$



Experiment No	Iron preparations	Rationale	No of Subjects	% Absorbed
19	Hemin Methyl ester (250 mg) in ordinary capsules	Kesterification of hemin gave the diester which was shown on Sephadex to have a molecular weight of 700 indicating it existed as a monomer in organic solvents	4	$0.2 \pm 0.1$
20 A	Hemin methyl ester (250 mg) in vegetable oil (7 ml)	Diester mixed with vegetable oil in which it was partially soluble could result in improved iron absorption	4	$0.2 \pm 0.11$ (for diester suspended in oil)
20 B			2	5.7 - 12.3 (diester soluble in oil)
21	Hemin sodium salt 50 mg Sodium bicarbonate 50 mg taken with water 90 ml	Hemin sodium salt readily soluble in water (pH 7). This sodium salt could result in improved absorption compared to hemin	4	$0.5 \pm 0.5$
22	Hemin sodium salt 250 mg Sodium bicarbonate 50 mg in ordinary capsules	The sodium salt tested in capsule form	3	$3.6 \pm 1.9$
23	Hemin sodium salt 250 mg Sodium bicarbonate 50 mg	Sodium salt tested in enteric coated capsule form	4	$3.0 \pm 3.0$

Experiment No	Iron preparations	Rationale	No of Subjects	% Absorbed
16	Hemin 250 mg Glycine 680 mg Sodium Hydroxide 40 mg Histidine 100 mg In 10 ml of water pH 8	As 15 Administered with histidine Spectrometric studies shows a significant sharpening of the hemin spectrum in glycine buffer containing histidine This sharpening was attributed to monomerization of hemin in solution	3	31 ± 1.6
17	Hemin 250 mg Glycine 680 mg Sodium Hydroxide 40 mg Xylitol penta-nicotinate 400 mg In 10 ml of water pH 8	As 15 Administered with xylitol penta-nicotinate as a source of nicotinic acid	4	22 ± 1.3
18	Hemin 250 mg Glycine 680 mg Sodium Hydroxide 40 mg Ascorbic Acid 400 mg In 10 ml of water pH 8	As 16 Administered with ascorbic acid	3	11 ± 0.3

# REFERENCES

- Antonini E Hemoglobin and myoglobin; their reactions with ligands - Frontiers of Biology North Holland Amsterdam 1971 pp 59-86
- Bauer G and Ehrenberg A Acta Chem Scand 17 8 1963
- Conrad, M E Benjamin, B I Williams, H L et al Gastroenterology 53: 5 1967 a.
- Conrad, M E Cortell S Williams, H L et al J Lab Clin Med 68 659 1967 b
- Ehrenberg A Acta Chem Scand 9 1183 1957
- Falk, J E Porphyrins and metalloporphyrins Elsevier Amsterdam 1967 pp 45 46 115, 118
- Fischer H In: Organic synthesis N L Drake, Ed Academic Press New York 1941 p 53
- Halberg L Harwerth, H -G and Vanotti A Eds Iron Deficiency Pathogenesis Clinical aspects - Therapy Academic Press London New York 1970
- Kellie, J Bioch J 80: 571 1985
- Kief, H Ed Iron metabolism and its disorders Excerpta Medica Amsterdam-Oxford American Elsevier Publishing Co Inc New York 1975
- Labbe, R and Nishida N Biochem Biophys Acta 26: 437 1967
- Larberg B In Hematin Enzymes Falk, J Larberg B Morton, R Eds Pergamon, New York 1961 p 76
- Reimann, F and Erdogan G Abstract XIII Int Congr Haematol Munich 1970 p 396
- Reizenstein, P Price D C Cronkite E P Cohn, S H and Wasserman, L Trans. Eur Soc Haematol 8: 237 1961
- Reizenstein, P WHO-report to Government of United Republic of Tanzania World Health Organization AFH/MUT/73 1974
- Reizenstein, P Annotation, Brit. J Haematol 31: 265, 1975 a
- Reizenstein, P J Sw Med. Assoc (Läkartidningen) 72: 4670 1975 b
- Reizenstein P Ehn, L. Forsberg K Högland, B and Liedén, G Sw J Nutr Res (Näringsforskning in Swedish) 1: 39 1975 c
- Reizenstein P Ehn, L. Forsberg A van Kuppevelt, A and Liedén, G In: Iron metabolism and its disorders H Kief, Ed Excerpta Int Medica Amsterdam-Oxford American Elsevier Publishing Co Inc New York, 1975 d

Experiment No	Iron preparations	Rationale	No of Subjects	% Absorbed
24	Hemin Sodium hydroxide 250 mg 40 mg	This experiment was carried out to study alkaline solution of heme	9	$65 \pm 3.9$
25	Hemin Milk of Magnesia 250 mg 10 ml	Milk of Magnesia has a pH 10 and it was felt that hemin given in this basic media could improve absorption	4	$33 \pm 1.4$
26	Hemin Sodium hydroxide Ascorbic acid taken in water 250 mg 40 mg 400 mg 20 ml	As study 24	1	87
27	Hemin ester Alcohol 88 Propylene glycol Sorbitol syrup Glycerin 250 mg 5 ml 2.5 ml 2.5 2.5	Soluble in lipid only	4	$0.3 \pm 0.65 (SE)$
28	Hemin ester Arachid oil 250 mg 10 ml	As study 27	4	$10.2 \pm 1.35 (SE)$

## Abstract

If hemoglobin or globin are to be used for food fortification, it becomes necessary to ascertain that the nutritional value of foods so fortified does not become unsatisfactory. The chemical score of isolated globin is as low as between 3 and 7 with isoleucine as the limiting amino-acid, and consequently the biological value (25.5) and net protein utilization (25.9) are also low. However, the true digestibility is high (101 per cent).

During the industrial processing, hemoglobin may be frozen, bleached or separated into heme and globin. Bleaching may reduce the digestibility and separation may cause the loss of some isoleucine, but these effects seem minor.

If cereals are fortified with about 1.5 per cent by weight of hemoglobin (supplying about 15 per cent of the nitrogen) the biological value of the cereals is improved by about 30 per cent. When meat products fortified with 1-10 per cent by weight of hemoglobin (supplying about 4-23 per cent of the proteins) were included in meals, the meals had chemical scores over 90 which is well acceptable.

## CHEMICAL SCORE

It is known that blood proteins have a relatively low chemical score (FAO 1970, van Kuppevelt et al 1976). The low chemical score is caused by an isoleucine-leucine imbalance. This is true both for plasma proteins and, particularly, for globin. Nevertheless plasma proteins are used extensively in Sweden in making meat products, in part for economic reasons, in part because they have favorable physico-chemical properties, and in part because they make it economically feasible to reduce the high fat content in Swedish meat products.

## EVALUATION OF FORMULATED FOODS AND PROTEIN EXTENDERS

Gopalan et al (1960-1975) found that under extreme conditions pellagra-like symptoms can be caused by a reduced isoleucine and a high leucine intake. This is true both in animals (so-called canine black tongue) and in some pellagra patients.

Darby and Hambræus (1975) have pointed out the responsibility of producers and authorities in studying the nutritional value of formulated foods and protein extenders. For this reason the nutritional value of globin was studied (van Kuppevelt et al 1976, Löfgren et al in press).

Takkunen, H Scand J Haematol Suppl 25 1976

Teale F W J Blochem Biophys Acta 35 543 1959

Yonstant T J Biol Chem 242 500 1967

## Acknowledgments

This work would have been impossible without the assistance of Mr B. Carlmark, B. Sc. Hematology Laboratory, Karolinska Hospital, who performed the iron absorption measurements and many statistical analyses, and Mr Gareth Lloyd-Jones, formerly at Sterling Winthrop Research & Development Division, Newcastle upon Tyne, England, who prepared the heme compounds studied. I am grateful to Prof. K. G. Paul for reading ch. III. The assistance of many collaborators in the Hematology Division (Mrs J. Berman, L. Ehn, K. Forsberg, A. v. Kuppevelt, and Tony Terpetra) is gratefully acknowledged. The collaboration with the Swedish Meat Research Institute, the Sterling Winthrop Research Institute, and the Departments of Nutrition, Stockholm and Uppsala Universities is gratefully acknowledged. The present work was supported by grants from the Swedish Council for Technological Development (STU), the Swedish Agricultural Council (Statens Jordbruksnämnd) and the Playtex-Wallace Co.

Biological value, total digestibility, and net protein utilization of globin Van Kuppevelt et al (1976) performed amino acid analyses of globin prepared by three different preparation methods. He could confirm earlier findings of a leucin isoleucin imbalance and he could demonstrate minor losses of some amino acids during preparation.

The limiting amino acid in blood protein is isoleucin. In contrast blood protein contains reasonable amounts of lysine, the limiting amino acid in most cereals. For this reason van Kuppevelt (1976) also studied the nutritional values of mixtures of cereals and blood proteins.

He found the expected low chemical score (between 3 and 10) and biological value (between 21 and 36) in globin and a similarly low net protein utilization (between 18 and 31). However, in various protein-cereal mixtures both the chemical scores and the biological values were up to 30 per cent higher than in either blood proteins or cereals alone. The optimum was found when 18-20 per cent of the total nitrogen and 1.4-1.7 per cent of the dry weight were derived from blood proteins. The possibility of fortification of wheat and other cereals with blood proteins was therefore raised in van Kuppevelt's article.

A similar study was performed by Löwgran et al (in press) who however studied industrially produced blood proteins rather than those produced in the laboratory and realistic composite meals rather than protein-cereal mixtures. In these studies also biological values and net protein utilizations were low, both for bleached hemoglobin (21.3 and 18.4 respectively), freeze-dried red cells (34.7 and 31.4) and for isolated globin (25.5 and 25.9). Total digestibilities were 85.5, 90.5 and 101% for the three preparations.

However, all of the three meals studied had a satisfactory chemical score (between 80 and 100) when meat products included in the meals were fortified with up to 10 per cent blood protein. The industrially produced blood protein fractions thus did not differ significantly from those produced in the laboratory, with the exception of chemically bleached hemoglobin, intended for use as a protein extender. Bleached hemoglobin has an apparent but not statistically significantly reduced absorbability.

In conclusion, globin and other blood proteins have low nutritional values and are unsuitable as staple foods or main components of diets, but well suited to be used as protein extenders in formulated foods and as protein extenders in mixed diets.

## REFERENCES

- Darby W and Hambræus L. Sw J Nutr Res (Näringsforskning) 19: 113, 1975.  
FAO Food Policy and Food Science Service, Nutrition Division, FAO, Rome, 1970.  
Gopalan C and Rao K S J. Vit and horm 33: 605, 1975.  
Gopalan, C and Srikantra N. Lancet 1: 954, 1960.  
Van Kuppevelt A, Levin G and Reizenstein P. Nutrition Reports International 13: 429, 1976.  
Löwgran M, Reizenstein P and Hambræus L. Nutritional value of blood proteins. Submitted to Sw J Nutr Res (Näringsforskning in Swedish).







# **Acta Medica Scandinavica**

**Supplementum 830**

3902

## **Application and Evaluation of Automated Arrhythmia Monitoring in the Coronary Care Unit**

**By Johan Hulting**

# Acta Medica Scandinavica

originally published as *Nordiskt Medicinskt Arkiv* was founded in 1869 by Professor Axel Key MD. In 1901 (from volume 34) this journal was divided into a medical and a surgical section. Since 1919 (from volume 52) the medical section has been published under the name of *Acta Medica Scandinavica*.

## *Acta Medica Scandinavica*

publishes papers on general medicine mainly from Denmark, Finland, Iceland, Norway, Sweden and the Netherlands. Short preliminary reports (not exceeding two pages) will be published at short notice. The papers are published in English, French or German. *Acta Medica Scandinavica* is published on a non-profit basis.

## *Subscriptions*

to *Acta Medica Scandinavica* (two volumes of six numbers each annually) include free supplements to the current volumes.

## *Subscription Rates*

Per annum = two volumes

In Denmark, Finland, Iceland, Norway, Sweden and the Netherlands Sw. cr. 330 incl. postage. Swedish subscribers add VAT.

Other countries Sw. cr. 375 incl. postage.

## *Chief Editor*

Professor Jan G. Waldenström MD  
*Acta Medica Scandinavica*  
Kungsgatan 54  
S-111 35 Stockholm, Sweden

## *Editorial Office*

*Acta Medica Scandinavica*  
Kungsgatan 54  
S-111 35 Stockholm, Sweden  
(All correspondence concerning manuscripts and editorial matters)  
Telephone 08/21 77 63

## *Subscription, Distribution and Advertising*

The Almqvist & Wiksell Periodical Company  
Gamla Brogatan 26, Box 62  
S-101 20 Stockholm 1, Sweden

## *Printers*

Almqvist & Wiksell Tryckeri AB  
S-751 81 Uppsala, Sweden

Departments of Medicine at Södersjukhuset, Karolinska Institutet  
Stockholm and Department of Medical Informatics Linköping  
University Linköping Sweden

APPLICATION AND EVALUATION OF  
AUTOMATED ARRHYTHMIA MONITORING  
IN THE CORONARY CARE UNIT

Johan Bulting





Shouldn't there be a patient  
here somewhere nurse?

This thesis is based mainly on the following papers

- I     Hulting J & Nygårds M -E    Evaluation of a computer-based system for detecting ventricular arrhythmias  
Acta Med Scand 199 56-60    1976
- II    Hulting, J    Blomqvist P & Nygårds M -E    Computer-based ECG analysis in acute myocardial infarction  
A comparison between two computer programs for the detection of ventricular arrhythmias    Acta Med Scand 201 439-447    1977
- III   Hulting, J & Nygårds M -E    Accuracy of alarms from a computer-based arrhythmia monitoring system    Acta Med Scand 203 153-159    1978
- IV    Hulting J    Detection of asystole ventricular fibrillation and ventricular tachycardia with automated ECG monitoring    Acta Med Scand (accepted for publication)
- V     Nygårds M -E & Hulting J    A system for automated ECG monitoring    Comp Biomed Res (accepted for publication)
- VI    Hulting J    Arrhythmias in the coronary care unit recognized with the aid of automated ECG monitoring  
A twelve-month study in 679 patients    Acta Med Scand (submitted for publication)

The above papers will be referred to by their Roman numerals I - VI



# CONTENTS

Abbreviations and definitions	7
Introduction	9
The aim of the present study	11
Special purpose arrhythmia detectors	13
Computer programs for arrhythmia detection	15
Arrhythmia detector and monitoring system evaluated in the present study	16
Ventricular beat (VB) detection by correlation of abnormal beats with a fixed VB waveform (Program I)	18
Arrhythmia classification with the use of QRS-T basis functions and power spectrum of the ECG (Program II)	20
An automated arrhythmia monitoring system based on Program II	23
System configuration	23
Alarm conditions	25
Status and alarm presentation	25
Interactive procedures	28
Discussion	28
Evaluation of the present arrhythmia detector and monitoring system	30
Principal aspects on evaluational problems	30
Evaluation of Program I	32
Comparison between Program I and Program II	34
Evaluation of arrhythmia alarms from a monitoring system based on Program II	38
Performance of the monitoring system in asystole, ventricular fibrillation and ventricular tachycardia	43
Discussion	46

Review of reported evaluations of other arrhythmia detectors and monitoring systems	49
Arrhythmias detected with the present monitoring system during long-term use	52
Interpretation test	59
Some other aspects of automated arrhythmia monitoring with the present system	62
Placement of electrodes and desirable configuration of ECG complexes	62
Starting monitoring	64
Technical problems	64
Modifications in the computer program	64
Education of personnel	65
ECG monitoring in patients with external pacemakers and with other special rhythms	65
Effects on arrhythmia documentation and patient care	66
Nurses' opinion on the system	67
Summary	68
Acknowledgements	71
References	72

## ABBREVIATIONS

AMI	Acute myocardial infarction
BBB	Bundle branch block
CCU	Coronary care unit
ECG	Electrocardiogram electrocardiographic
HR	Heart rate
PVB	Premature ventricular ectopic beat
SR	Sinus rhythm
SVB	Supraventricular ectopic beat
SVT	Paroxysmal supraventricular tachycardia
VB	Ventricular ectopic beat
VF	Ventricular fibrillation
VT	Ventricular tachycardia

## DEFINITIONS

This text contains terms used in medical computer technology  
Definition and explanation of some terms have been collected below

- Algorithm** A set of rules for the solution of a problem in a finite number of steps
- Analog computer technique** Computational quantities represented by physical quantities usually voltages
- Arrhythmia detector** Central part of an arrhythmia monitoring system Analyses each waveform of the incoming ECG signal The detector produces notes regarding specific events in the ECG or information regarding the present state of the signal e.g heart rate background rhythm and artefacts
- Basis functions representation** Representing a whole class of functions with its inherent components When added together with proper amplitudes these components or basis functions will reproduce any member of the class
- Digital computer technique** Computational quantities represented by binary numbers

Discriminant function analysis Statistical technique for studying differences between populations. Can also be used to learn which combination of measurements best separates the populations.

Monitoring system Administers, stores, and presents data generated by one or more arrhythmia detectors.

Orthogonal basis functions Basis functions which are both orthogonal and normal. i.e. the average product of corresponding points in any pair of different functions should be zero, whereas the average product of any function with itself should be unity.

Power spectrum The power of a signal computed for each frequency component within the signal.

## INTRODUCTION

Acute myocardial infarction (AMI) is an important cause of morbidity and mortality. AMI was associated with a hospital mortality between 16 and 34% in a Swedish multicenter study (Henning & Lundman 1975). However, a significant proportion of patients with AMI die suddenly before reaching the hospital (Wiklund 1971). Unexpected deaths in or outside hospital are usually caused by arrhythmias, probably ventricular fibrillation (VF) (Lown et al 1969, Liberman et al 1974). This and some other serious arrhythmias can be reverted to normal by electric countershock as demonstrated by Zoll et al (1956) and Lown et al (1962). For proper treatment of arrhythmias the ECG must be available. Continuous ECG monitoring of cardiac patients and active treatment of arrhythmias were introduced in the early 60's (Day 1963, Brown et al 1963, Julian et al 1964, Meltzer & Mitchell 1966). Two controlled studies have shown that such coronary care in AMI lowered the hospital mortality about 50% and this reduction was statistically significant (Christiansen et al 1971, Hofvendal 1971). The beneficial effect of treatment in a coronary care unit (CCU) compared to treatment in ordinary hospital wards remained significant up to three years after discharge from hospital (Hofvendal 1971).

Conventional ECG monitoring in the CCU utilizes bedside amplifiers and oscilloscopes that are connected to multichannel visual displays centrally. Optimally the nurses perform round the clock surveillance of oscilloscope screens but personnel resources usually do not permit constant human observation. Even so it is obvious that attention fluctuates markedly during the day. To improve the ECG monitoring heart rate (HR) alarms have been added. The ratemeter alarm alerts the staff when HR deviates outside preset limits. The HR alarm system usually detects the most serious arrhythmias such as asystole and VF.

In some patients signal artefacts including muscle potentials give rise to numerous false tachycardia alarms. Frequent false bradycardia alarms occur in patients with low amplitude ECG complexes. Also the HR system is insensitive to brief slow or fast rhythm changes due to a built-in time constant. Neither a sudden conduction disturbance nor a rhythm change that falls within the HR limits of the system is detected. The efficiency of the HR system alone in ECG monitoring has not been critically evaluated. In one report only 10 out of 167 HR

Discriminant function analysis Statistical technique for studying differences between populations. Can also be used to learn which combination of measurements best separates the populations.

Monitoring system Administers, stores, and presents data generated by one or more arrhythmia detectors.

Orthonormal basis functions Basis functions which are both orthogonal and normal, i.e., the average product of corresponding points in any pair of different functions should be zero, whereas the average product of any function with itself should be unity.

Power spectrum The power of a signal computed for each frequency component within the signal.

## INTRODUCTION

Acute myocardial infarction (AMI) is an important cause of morbidity and mortality. AMI was associated with a hospital mortality between 16 and 34% in a Swedish multicenter study (Henning & Lundman 1975). However, a significant proportion of patients with AMI die suddenly before reaching the hospital (Wiklund 1971). Unexpected deaths in or outside hospital are usually caused by arrhythmias, probably ventricular fibrillation (VF) (Lown et al 1969, Libérthson et al 1974). This and some other serious arrhythmias can be reverted to normal by electric counterstroke as demonstrated by Zoll et al (1956) and Lown et al (1962). For proper treatment of arrhythmias the ECG must be available. Continuous ECG monitoring of cardiac patients and active treatment of arrhythmias were introduced in the early 60's (Day 1963, Brown et al 1963, Julian et al 1964, Heltzer & Kitchell 1966). Two controlled studies have shown that such coronary care in AMI lowered the hospital mortality about 50% and this reduction was statistically significant (Christiansen et al 1971, Hofvendal 1971). The beneficial effect of treatment in a coronary care unit (CCU) compared to treatment in ordinary hospital wards remained significant up to three years after discharge from hospital (Hofvendal 1971).

Conventional ECG monitoring in the CCU utilizes bedside amplifiers and oscilloscopes that are connected to multichannel visual displays centrally. Optimally the nurses perform round the clock surveillance of oscilloscope screens but personnel resources usually do not permit constant human observation. Even so it is obvious that attention fluctuates markedly during the day. To improve the ECG monitoring heart rate (HR) alarms have been added. The ratemeter alarm alerts the staff when HR deviates outside preset limits. The HR alarm system usually detects the most serious arrhythmias such as asystole and VF.

In some patients signal artefacts including muscle potentials give rise to numerous false tachycardia alarms. Frequent false bradycardia alarms occur in patients with low amplitude ECG complexes. Also the HR system is insensitive to brief slow or fast rhythm changes due to a built in time constant. Neither a sudden conduction disturbance nor a rhythm change that falls within the HR limits of the system is detected. The efficiency of the HR system alone in ECG monitoring has not been critically evaluated. In one report only 10 out of 167 HR

alarms observed during 200 h of monitoring were true tachy- or bradycardia alarms (Frost et al 1977) The HR alarm system usually activates a paper chart recorder presenting the ECG at an alarm but because of the time constant this record never shows the initial part of the alarm-generating event Therefore most manufacturers have incorporated a memory loop into their system Constant recording and erasing of the ECG from each patient in the unit is performed At an alarm the ECG preceding the alarm can be presented A better method for arrhythmia documentation is a slow speed continuous ECG recording from all patients in the CCU with the use of a multichannel recorder (MacMillan et al 1967 Mogensen 1970) However a thorough analysis of all the data produced is very time-consuming

The accuracy of routine nurses-based arrhythmia monitoring has been tested in a few studies (Mogensen 1970 Romhilt et al 1973 Lindsay & Bruckner 1975 Vetter & Julian 1975, Holmberg et al 1977) The methods used for establishing the true arrhythmia incidence and prevalence as well as the length of the test periods differed markedly between the investigators Thus it is difficult to compare the abovementioned studies Mogensen (1970) found that the nurses detected about 25% of all episodes of ventricular tachycardia (more than 2 ventricular ectopic beats (VBs) in succession with a rate  $>100/\text{min}$ ) and about 50% of all patients with this arrhythmia during the first 24 h in the CCU A similar observation was made by Ryden et al (1975) Romhilt et al (1973) showed that conventional monitoring detected about 20% of the patients fulfilling criteria given by Lown et al (1967) for prophylactic treatment with lidocaine in order to prevent VF in AMI Also there was a marked time delay between the first true arrhythmia episode and the first arrhythmia detected by the nurses

A proper quantification of arrhythmias is difficult with the conventional oscilloscope monitoring technique This can be a disadvantage in antiarrhythmic treatment Even though memory oscilloscopes are now used in many CCUs the time available for the human observer may be too short to permit an accurate arrhythmia diagnosis The constant observation of oscilloscope screens is boring and probably one important reason for the difficulties in recruiting nurses to the CCU High quality conventional monitoring is expensive since it requires a large and well trained staff



The need for improved methods for arrhythmia monitoring has been emphasized earlier (DeSanotis et al 1972 Foxzard 1973 Vaisrub 1975). In order to improve the standards of ECG monitoring and to reduce the monitoring demands on the staff great efforts have been made to develop automated monitoring systems. Such systems based on digital computer technique also permit rational methods for the storage and presentation of data.

In this study a computer-based arrhythmia monitoring system for the CCU will be presented and discussed. The present version of the system installed in the CCU of Södersjukhuset, Stockholm, has been developed in close co-operation with the Department of Medical Information at Linköping University.

The present monitoring system constitutes one part of a larger project for the application of computers in clinical medicine. The work on

ECG monitoring was commenced in 1970. A QRS detector based on analog technique was constructed in 1972. The principles for arrhythmia detection were implemented into a digital computer in the following year. The various stages during development and evaluation are shown in Fig. 1.

The aim of the present study may be summarized as follows:

- 1 To present and discuss the development of an automated arrhythmia monitoring system for the CCU (I, II and V)
- 2 To evaluate this system in various arrhythmias occurring during CCU monitoring (III and IV)
- 3 To use the automated monitoring system as an aid for the study of arrhythmias in a large number of CCU patients (VI)
- 4 To improve knowledge regarding the clinical relevance or prognostic value of arrhythmias detected by the system (VI)

Computer-assisted analysis of ambulatory ECG recordings and automated arrhythmia interpretation of the diagnostic ECG are not within the scope of this study.

alarms observed during 200 h of monitoring were true tachy- or bradycardia alarms (Frost et al 1977). The HR alarm system usually activates a paper chart recorder presenting the ECG at an alarm but because of the time constant this record never shows the initial part of the alarm-generating event. Therefore most manufacturers have incorporated a memory loop into their system. Constant recording and erasing of the ECG from each patient in the unit is performed. At an alarm the ECG preceding the alarm can be presented. A better method for arrhythmia documentation is a slow speed continuous ECG recording from all patients in the CCU with the use of a multichannel recorder (MacMillan et al 1967, Mogensen 1970). However a thorough analysis of all the data produced is very time-consuming.

The accuracy of routine nurses-based arrhythmia monitoring has been tested in a few studies (Mogensen 1970, Romhilt et al 1973, Lindsay & Bruckner 1975, Vetter & Julian 1975, Holmberg et al 1977). The methods used for establishing the true arrhythmia incidence and prevalence as well as the length of the test periods differed markedly between the investigators. Thus it is difficult to compare the abovementioned studies. Mogensen (1970) found that the nurses detected about 25% of all episodes of ventricular tachycardia (more than 2 ventricular ectopic beats (VBs) in succession with a rate  $>100/\text{min}$ ) and about 50% of all patients with this arrhythmia during the first 24 h in the CCU. A similar observation was made by Rydén et al (1975). Romhilt et al (1973) showed that conventional monitoring detected about 20% of the patients fulfilling criteria given by Lown et al (1967) for prophylactic treatment with lidocaine in order to prevent VF in AMI. Also there was a marked time delay between the first true arrhythmia episode and the first arrhythmia detected by the nurses.

A proper quantification of arrhythmias is difficult with the conventional oscilloscope monitoring technique. This can be a disadvantage in antiarrhythmic treatment. Even though memory oscilloscopes are now used in many CCUs the time available for the human observer may be too short to permit an accurate arrhythmia diagnosis. The constant observation of oscilloscope screens is boring and probably one important reason for the difficulties in recruiting nurses to the CCU. High quality conventional monitoring is expensive since it requires a large and well trained staff.

## SPECIAL PURPOSE ARRHYTHMIA DETECTORS

In the special purpose arrhythmia detector all signal analysis is performed in electronic circuits specially designed for this purpose and serving one patient at a time. Depending on the function of these circuits various characteristics of the signal may be recognized and used for beat separation and classification. Detector output is either proportional e.g. to HR or in the form of electric impulses e.g. one for each VB detected by the system. Most of the older detectors work with analog technique. Some of the monitors are hybrid performing both analog and digital signal processing.

The simplest special purpose detector is the HR-meter. In the process of improving the ratemeter the early work by Haber (1959) resulted in an arrhythmia detector that recognized abnormal beats from changes in HR and prolongations in the QRS interval. Others performed arrhythmia analysis and classification solely on the basis of R-R interval analysis (Wacher et al 1971; Stinton et al 1972; Rempelman et al 1977; Pantem et al 1977). The difference in QRS area between an adaptive reference complex and each new waveform was used in an arrhythmia detector constructed by Neilson (1974). Kozdi et al (1968) separated normal and abnormal beats by a cross correlation technique. Detection of aberrant beats by comparing the energy content of two frequency bands of the ECG signal has been devised and evaluated by Karlsson et al (1970). A method for the detection of early VBs (R-on-T VBs) has been described (Breithardt et al 1975) but there are no data as to its usefulness in clinical monitoring. A small portable analog detector suited mainly for use in ambulatory patients was described and tested by Cannon & Harrison (1974). Feazor et al (1970) developed a waveform analyzer in which abnormal beats were identified from amplitude criteria. In order to separate VBs from other beats and artefacts abnormal beats were correlated with a fixed VB waveform stored in the system. However no acceptable testing of this detector has been published. This last mentioned principle for arrhythmia analysis was implemented into the first version of the present arrhythmia monitor.

Although several special purpose detectors have been used in clinical practice they have not reached general acceptance. There are probably several reasons for this. Firstly various arrhythmias and

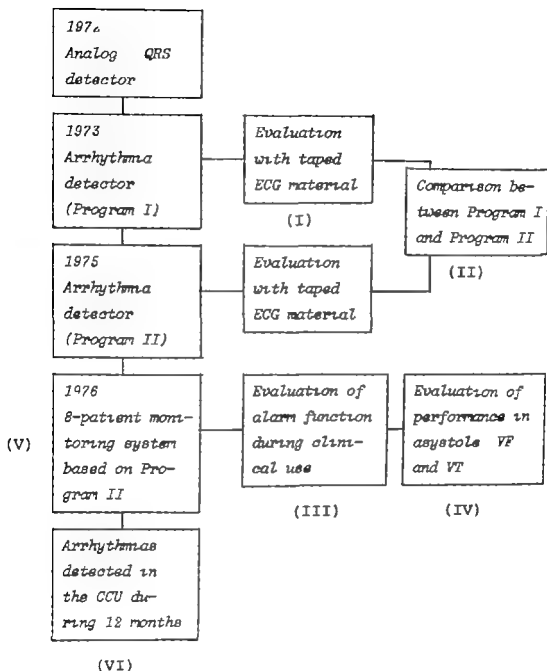


Fig. 1 Various stages during system development and evaluation

## COMPUTER PROGRAMS FOR ARRHYTHMIA DETECTION

The small digital computer (minicomputer) with its flexibility : great computational capacity and relatively low price has opened the field for advanced arrhythmia monitoring in the CCU. Also one computer may analyse the ECG from several patients simultaneously. The initial expectations however were too optimistic and progress during the last decade has been relatively slow. Early algorithms that worked in the laboratory did not perform equally well during routine CCU monitoring.

In the digital systems the ECG signal is sampled with a rate between 100 and 500 Hz. Methods for the reduction and the detection of artefacts have been omitted from this brief description. In the next stage of the analysis QRS detection is performed usually from the derivative of the signal (first difference of sample points). A possible QRS complex can be handled in several different ways. Some systems perform a direct comparison/correlation with a stored normal for the patient. In other systems certain characteristics (features) from each complex are extracted. In Table I the principles for some arrhythmia detectors and monitoring systems described and evaluated in the scientific literature are presented. For proper functioning of the detector the stored normal waveform must adapt itself to slow spontaneous changes in the shape of the ordinary QRS complexes. Abnormal complexes may be correlated to previously detected and manually classified beats (Feldman et al 1971) to a fixed stored prototype VB waveform (Wigertz et al 1974) or to previously detected and stored families of abnormal complexes (Shah et al 1977). This correlation aims at a separation between normal beats, SVBs, VBs and various artefacts. Bultgren et al (1975) evaluated a monitoring system which separated abnormal beats from normal ones with the use of a correlation technique and/or R-R analysis.

In most detectors and monitoring systems in Table I some kind of data compression is performed in order to make it possible to handle the enormous amount of data that is fed into the computer. A useful data reducing preprocessing algorithm reported by Cox et al (1968) has reached wide-spread use. With this algorithm called *Astec* (amplitude-tone-time-epoch-coding) the ECG signal is transformed into

artefacts in clinical monitoring are too variable to be handled satisfactorily by these relatively simple devices. As a consequence results from thorough evaluations are lacking for most detectors and no long-term clinical evaluation study has been presented, with the exception of a study by Vetter & Julian (1975). This will be referred to on page 50. Secondly most special purpose detectors rely on individual control of parameter settings. This puts unacceptable demands on the staff in a multipatient system.

## COMPUTER PROGRAMS FOR ARRHYTHMIA DETECTION

The small digital computer (minicomputer) with its flexibility great computational capacity and relatively low price has opened the field for advanced arrhythmia monitoring in the CCU. Also one computer may analyze the ECG from several patients simultaneously. The initial expectations however were too optimistic and progress during the last decade has been relatively slow. Early algorithms that worked in the laboratory did not perform equally well during routine CCU monitoring.

In the digital systems the ECG signal is sampled with a rate between 100 and 500 Hz. Methods for the reduction and the detection of artefacts have been omitted from this brief description. In the next stage of the analysis QRS detection is performed usually from the derivative of the signal (first difference of sample points). A possible QRS complex can be handled in several different ways. Some systems perform a direct comparison/correlation with a stored normal for the patient. In other systems certain characteristics (features) from each complex are extracted. In Table I the principles for some arrhythmia detectors and monitoring systems described and evaluated in the scientific literature are presented. For proper functioning of the detector the stored normal waveform must adapt itself to slow spontaneous changes in the shape of the ordinary QRS complexes. Abnormal complexes may be correlated to previously detected and manually classified beats (Feldman et al 1971) to a fixed stored prototype VB waveform (Wigertz et al 1974) or to previously detected and stored families of abnormal complexes (Shah et al 1977). This correlation aims at a separation between normal beats, SVBs, VBs and various artefacts. Hultgren et al (1975) evaluated a monitoring system which separated abnormal beats from normal ones with the use of a correlation technique and/or R-R analysis.

In most detectors and monitoring systems in Table I some kind of data compression is performed in order to make it possible to handle the enormous amount of data that is fed into the computer. A useful data reducing preprocessing algorithm reported by Cox et al (1968) has reached wide-spread use. With this algorithm called 'Artec' (amplitude-time-speech-coding) the ECG signal is transformed into

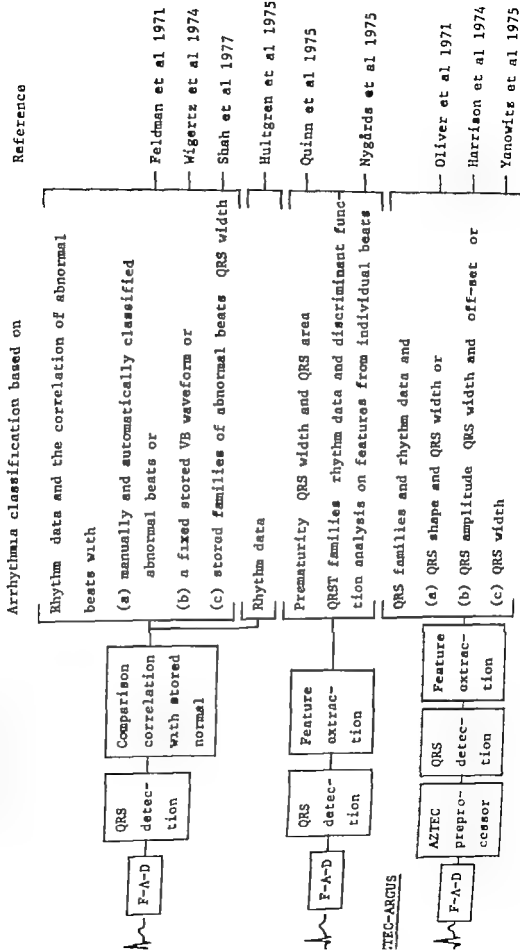
artefacts in clinical monitoring are too variable to be handled satisfactorily by these relatively simple devices. As a consequence results from thorough evaluations are lacking for most detectors and no long-term clinical evaluation study has been presented with the exception of a study by Vetter & Julian (1975). This will be referred to on page 50. Secondly most special purpose detectors rely on individual control of parameter settings. This puts unacceptable demands on the staff in a multipatient system.



horizontal lines and slopes. In the further analysis each complex is characterized with respect to amplitude width and shape. In a following step complexes with similar shapes are grouped together. In the final classification of a complex rhythm data such as prematurity and compensatory pause are also considered. The above principles of arrhythmia detection (ARGUS Arrhythmia Guard System) have been implemented into some systems (Oliver et al 1971, Harrison et al 1974, Yanowitz et al 1974). A modified Argus system has been described by Zeelenberg et al (1977). Other features that have been used in arrhythmia detectors are QRS width and QRS area (Quinn et al 1975). An effective method for feature extraction should allow adequate waveform characterization with a minimum of parameters. In the final version of our own monitoring system the method used made it possible to represent the entire QRS-T complex from five parameters (7).

Ideally a monitoring system should work with a minimum of operator (nurse) interference. The method should be relatively insensitive to minor or moderate disturbances in the ECG signal occurring during clinical monitoring.

The great variability in rhythm beat shapes and artefacts calls for modifications of arrhythmia algorithms during the developmental stage. Such changes in the programs must rely on thorough evaluation studies. Changes in one part of the program however may add new problems to other sites.

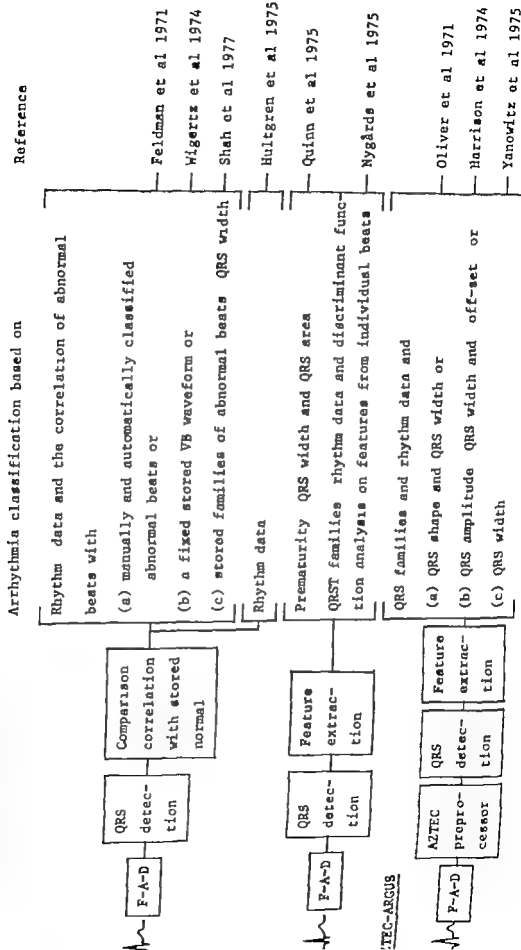


horizontal lines and slopes. In the further analysis each complex is characterized with respect to amplitude, width and shape. In a following step complexes with similar shapes are grouped together. In the final classification of a complex, rhythm data such as prematurity and compensatory pause are also considered. The above principles of arrhythmia detection (ARGUS Arrhythmia Guard System) have been implemented into some systems (Oliver et al 1971; Harrison et al 1974; Yanowitz et al 1974). A modified Argus system has been described by Zeelenberg et al (1977). Other features that have been used in arrhythmia detectors are QRS width and QRS area (Quinn et al 1975). An effective method for feature extraction should allow adequate waveform characterization with a minimum of parameters. In the final version of our own monitoring system the method used made it possible to represent the entire QRS complex from five parameters (V).

Ideally a monitoring system should work with a minimum of operator (nurse) interference. The method should be relatively insensitive to minor or moderate disturbances in the ECG signal occurring during clinical monitoring.

The great variability in rhythms, beat shapes and artefacts calls for modifications of arrhythmia algorithms during the developmental stage. Such changes in the programs must rely on thorough evaluation studies. Changes in one part of the program however may add new problems to other sites.

Figure 1 Principles for some digital arrhythmia detectors and monitoring systems: F-A-D = Filtering and artefact detecting steps and analog to digital conversion



horizontal lines and slopes. In the further analysis each complex is characterized with respect to amplitude width and shape. In a following step complexes with similar shapes are grouped together. In the final classification of a complex rhythm data such as prematurity and compensatory pause are also considered. The above principles of arrhythmia detection (ARGUS Arrhythmia Guard System) have been implemented into some systems (Oliver et al 1971, Harrison et al 1974, Yanowitz et al 1974). A modified Argus system has been described by Zeelenberg et al (1977). Other features that have been used in arrhythmia detectors are QRS width and QRS area (Quinn et al 1975). An effective method for feature extraction should allow adequate waveform characterization with a minimum of parameters. In the final version of our own monitoring system the method used made it possible to represent the entire QRS complex from five parameters (V).

Ideally a monitoring system should work with a minimum of operator (nurses) interference. The method should be relatively insensitive to minor or moderate disturbances in the ECG signal occurring during clinical monitoring.

The great variability in rhythm beat shapes and artefacts calls for modifications of arrhythmia algorithms during the developmental stage. Such changes in the programs must rely on thorough evaluation studies. Changes in one part of the program however may add new problems to other sites.

## ARRHYTHMIA DETECTOR AND MONITORING SYSTEM EVALUATED IN THE PRESENT STUDY

The two methods for arrhythmia analysis in the CCU used in the present study will be described in some detail and complement the principal aspects mentioned in the previous section

### VENTRICULAR BEAT (VB) DETECTION BY CORRELATION OF ABNORMAL BEATS WITH A FIXED VB WAVEFORM (PROGRAM I)

A 16-bit minicomputer (Datacube D5/30) with 16 K words of core memory was used in the first arrhythmia detector. The arrhythmia program provided a beat-by-beat real-time analysis of the ECG. The program organization is illustrated in Fig. 2.

Sampling and R wave recognition. The sampling program had the highest priority and was executed every 10th ms. After digital low pass filtering (30 Hz cut off) the differences between sample points of the ECG were computed and stored in a circular memory of 512 8-bit words. Artefact detection was also performed and permitted automatic rejection of low-quality ECG portions. Whenever the derivative of the ECG signal or a base line shift exceeded certain limits the waveform analysis was blocked for 2 s. R wave recognition was performed using

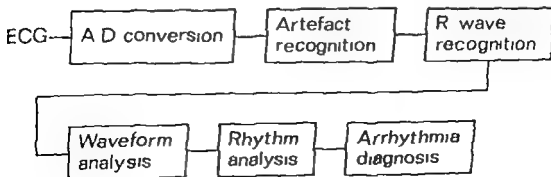
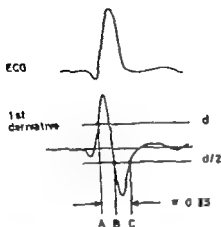
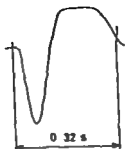


Fig. 2 Program organization in the first arrhythmia detector



**Fig. 3** Principles for R wave detection (Program I and II) For explanation of symbols see text



**Fig. 4** Prototype VB waveform (Program I)

an adaptive threshold ( $d$ ) for the difference between sample points. An R wave was detected when the following sequential criteria were fulfilled within 0.25 s: (A) positive difference exceeding threshold ( $d$ ) (B) negative difference exceeding threshold ( $d/2$ ) (C) signal returning to base line or difference below threshold ( $d/2$ ) (Fig. 3). At the detection of an R wave the previous R-R interval and the position in the memory were passed to the waveform analysis program.

**Waveform and rhythm analysis.** For each R wave 200 ms of sampled data were compared to the running average of the normal QRS complex for the patient. This reference complex was created at the onset of monitoring from the first 10 s of the ECG. A new complex was considered normal if the sum of absolute differences between corresponding sample points went below a certain limit. A beat classified as normal was added to the running average with a time constant corresponding to 32 beats. To separate VEs from artefacts and beats of supraventricular origin each abnormal complex was

## ARRHYTHMIA DETECTOR AND MONITORING SYSTEM EVALUATED IN THE PRESENT STUDY

The two methods for arrhythmia analysis in the CCU used in the present study will be described in some detail and complement the principal aspects mentioned in the previous section

### VENTRICULAR BEAT (VB) DETECTION BY CORRELATION OF ABNORMAL BEATS WITH A FIXED VB WAVEFORM (PROGRAM I)

A 16-bit minicomputer (Datasaab D5/30) with 16 K words of core memory was used in the first arrhythmia detector. The arrhythmia program provided a beat-by-beat real-time analysis of the ECG. The program organization is illustrated in Fig 2

Sampling and R wave recognition The sampling program had the highest priority and was executed every 10th ms. After digital low pass filtering (30 Hz cut off) the differences between sample points of the ECG were computed and stored in a circular memory of 512 8-bit words. Artefact detection was also performed and permitted automatic rejection of low-quality ECG portions. Whenever the derivative of the ECG signal or a base line shift exceeded certain limits the waveform analysis was blocked for 2 s. R wave recognition was performed using

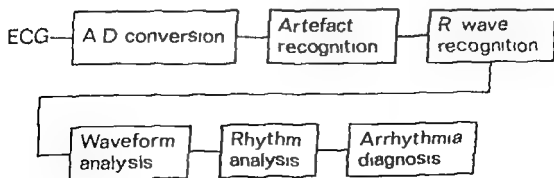


Fig. 2 Program organisation in the first arrhythmia detector (Program I)



described. However the inhibition of the analysis at a high level of artefacts was extended from 2 to 4 s.

A waveform recognized as a possible R wave was analysed further and classified into one of the following categories: normal beat, supraventricular beat (premature), ventricular beat, undefined beat or artefact. This procedure involved the following steps: feature extraction, grouping of waveforms, shape classification and final diagnosis.

Feature extraction. The QRS complex was represented as the sum of four approximately orthonormal basis signals. The basis signals, two for the QRS and two for the ST part of the complex, were mathematically represented by the Gaussian function and its first derivative (Fig. 6). In addition QRS width was computed whereas the distance between the QRS and the ST was predicted from HR according to Bazett (1920). Consequently five parameters were used to describe the morphology of each complex: the QRS width and the amplitudes of the four basis signals. The mean square error between the sample points of the original complex and the curve reconstructed from the parameters was

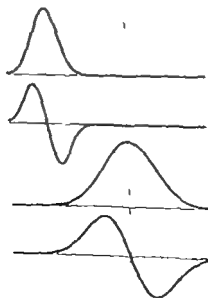


Fig. 6 Basis signals used for QRS representation (Program II)

correlated to a typical VB waveform (Fig 4) which had been derived from earlier ECG recordings. An abnormal complex was marked as ventricular if the absolute value of the normalized correlation coefficient between the complex and the stored VB exceeded 0.8. If the basic rhythm was regular, a waveform approved as ventricular was classified as a VB only if preceded by an R-R interval shorter than 90% of the running average and followed by a compensatory pause. The basic rhythm was considered regular if the running standard deviation of R-R intervals was less than 8% of the average R-R interval.

The above arrhythmia detector was tested on a taped ECG material (I) and also compared with a more complex method for arrhythmia analysis (II). Program I was implemented into a 4-patient monitoring system in 1974. This system however was not taken into routine use.

#### ARRHYTHMIA CLASSIFICATION WITH THE USE OF QRST BASIS FUNCTIONS AND POWER SPECTRUM OF THE ECG (PROGRAM II)

The program organization is shown in Fig 5.

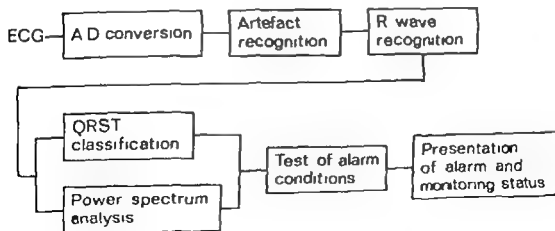


Fig. 5 Program organization in the second arrhythmia detector (Program II)

signal filtering and sampling rate were the same as in Program I. R

normal beat or if premature as a SVB with normal shape. The classification of an abnormal beat was considered preliminary until the next beat had been recognized.

Final diagnosis In this step prematurity and compensatory pause were combined with the shape classification. The final diagnosis was also influenced by basic rhythm and by the number of complexes in an abnormal waveform group as well as by the error in the parameterization procedure. The tests for prematurity and compensatory pause rested on a statistical basis utilizing the running average and covariance of R-R intervals of normal complexes. To further improve artefact suppression an index reflecting noise level was computed. This index was incremented at a failure of the parameterization and each time a new waveform group was created. Also an excessive baseline shift between adjacent QRS complexes added to the index which gradually returned to zero at the detection of undistorted normal beats. At a certain value of this index the classification of abnormal beats was blocked.

Power spectrum analysis A special subroutine to aid the recognition of VF, VT and asystole was entered at the detection of an abnormal ECG pattern lasting for 5 s in a signal free from major artefacts. This subroutine computed the power spectrum of the ECG. Asystole was diagnosed if the power of the signal did not exceed a certain limit and if no R waves had been detected during 5 s. VF and VT were differentiated from other conditions by searching a peak in the power spectrum between 1.7 and 9 Hz. If such a peak was found VT and VF were diagnosed from the peak frequency and the relative power of a frequency band including the peak.

## AN AUTOMATED ARRHYTHMIA MONITORING SYSTEM BASED ON PROGRAM II

### System configuration

Program II was incorporated into an 8 patient arrhythmia monitoring system that was gradually introduced to the personnel in 1976. The general configuration of the system is shown in Fig. 7. An extension of core memory of the minicomputer from 16 K to 28 K was necessary in order to allow multipatient monitoring, interactive procedures and

computed in order to estimate the precision of each parameterization. If this error exceeded a certain value the original complex was regarded as an artefact. In a later version of the program, however, a fifth basis signal corresponding to the second derivative of the Gaussian function was added to the original set when parameterization failed. This fifth basis signal was introduced in order to obtain a better representation of a QRS complex with a split R wave.

Waveform grouping Complexes with similar shapes as described by the waveform features were brought together. Each waveform group was characterized by the means and the standard deviations of five parameters transformed from the original set of four amplitude coefficients and one width parameter. The reference group comprised the waveform that dominated when monitoring was initiated. The grouping of subsequent beats was based on a distance measure in the five-dimensional feature space. A new group was created when the distance to the existing group(s) exceeded preset limits. However, a new group was considered preliminary until the number of complexes reached a certain threshold that was dependent on the noise level and the degree of shape aberration. The parameters of a complex were updated whenever a new complex was incorporated. A maximum of eight groups was allowed for each patient. Adjacent groups were put together at regular intervals and a group without new complexes during a certain period of time was deleted. To cope with sudden changes in the shape of the reference complex this was substituted for the presently dominant group if no new complexes had been assigned to the former group for about 2 min. If the difference between the new and the old reference waveform exceeded certain limits a message was delivered.

Preliminary waveform typing Waveforms not assigned to the reference group were separated into four categories: probable VBs, possible VBs, abnormal non-VBs, and essentially normal complexes. This classification was based on two linear discriminant functions operating on the features of the current waveform and if the rhythm was regular on the preceding R-R interval. The coefficients of these functions were set to minimize the probability of misclassification in a previous ECG material. This material was equivalent to that described earlier (1). A complex belonging to the reference group or classified as essentially normal in the above procedure was typed as a

return of power the system was automatically restarted

### Alarm conditions

At the detection of an abnormal ECG a number of alarm tests were performed. In Table II the various alarms associated with arrhythmias are listed and defined. Alarm limits for bradycardia, tachycardia and VB excess rate could be set individually but were automatically set to 50, 120 and 5/min respectively at the onset of monitoring. Alarm messages referring to the status of the ECG signal are shown in Table III. The alarm "what has happened?" however was reported at the detection of an abnormal ECG that fitted neither the criteria for noise nor those for an arrhythmia alarm.

### Status and alarm presentation

The upper part of the video screen was used for displaying HR, VB frequency, basic rhythm and alarm messages for each patient (Fig. 8). Alarms could be reset from bedside or the central station but automatic reset was performed after a certain time (usually 4 min) if the alarm condition was no longer present. The alarms were grouped into three priority levels:

- (1) Highest priority or "H" alarms. These messages resulted in a repetitive signal in the pocket receiver and a flashing red light at the bedside and in the central station.
- (2) Second priority or "S" alarms which were accompanied by a short sound and a steady light.
- (3) Lowest priority or "L" alarms. These messages were presented on the video screens without any additional alerting signals.

At arrhythmia alarms a write-out with an ECG signal delayed 5 s was recorded automatically at a speed of 10 mm/s and usually with a duration of 15 s.

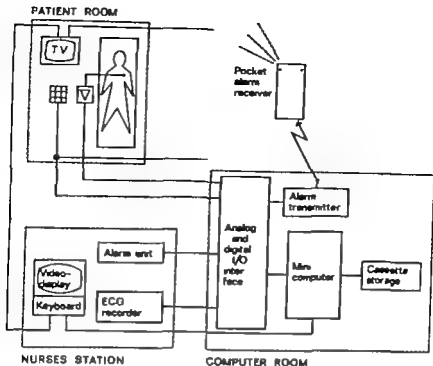


Fig. 7 Configuration of the monitoring system

data storage. A bipolar ECG with fixed amplification was obtained from standard bedside equipment. Monitoring on/off and alarm/reset controls were added to existing patient units. Monitoring status and arrhythmia alarms were presented on a video terminal in the nurses station with slave monitors in the patient rooms. A computer-controlled 2-channel ink-jet recorder in the central station was used to document the ECG causing an alarm. A wireless alarm transmitting system controlled by the computer was activated in special alarm situations and alerted the nurses who carried small pocket receivers. Interactive communication with the monitoring system was performed via the video terminal or handheld numeric keyboards at bedside.

All programs were loaded from a cassette tape unit. However, in case of power failure the content of the core memory remained intact and on

Table III Monitoring status alarms

Priority	Message	
**	WHAT HAS HAPPENED?	Abnormal pattern for 10 s in the absence of artefacts and no other condition applicable
**	CHECK LEADS	High level of artefacts for 30 s monitoring impossible
**	NEW QRS	New shape of reference complex rhythm unchanged
*	NOISY ECG	VB detection inhibited due to artefacts for at least 15 s of last min
*	CHANGE ELECTRODE PLACEMENT	Peaked P or T waves or narrow Q or S waves VB detection inhibited
*	LOW AMPLITUDE	Amplitude of normal QRS < 0.3 mV VB detection inhibited
*	BAD ELECTRODE CONTACT	Powerline interference

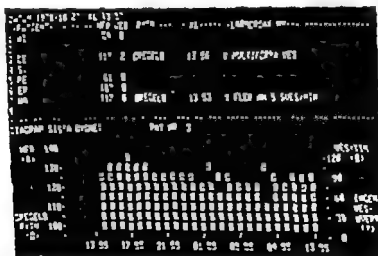


Fig. 3 Status and alarm display. On the upper part of the screen are shown name HR (HR) number of VEs (VES) during last minute and rhythm (RHYTHM: IRREGULAR) for each patient. Alarm messages appear to the right. Present display shows alarms for multiform VEs (patient 3) and more than 5 SVES/min (FLER RN 5 SVES/MIN) from patient 7. Below is seen a trend plot from patient 3 with HR and VB frequency for the last 23 h.

Table II Arrhythmia alarms

Priority	Message	Explanation
***	ASYSTOLE	R-R > 5 0 s and power below threshold
***	VENTRICULAR FIBRILLATION	Abnormal pattern for 5 s and peak in power spectrum
***	VENTRICULAR TACHYCARDIA	More than 3 consecutive VBs and rate >120/min or narrow peak in power spectrum
**	RUN OF MORE THAN 3 VB S	More than 3 consecutive VBs with rate $\leq$ 120/min
**	IDIOVENTRICULAR RHYTHM	More than 3 consecutive VBs with rate $\leq$ 40/min or QRS width >0 14 s and HR $\leq$ 40/min
**	BRADYCARDIA	HR more than 15 beats/min below bradycardia limit
**	TACHYCARDIA	HR more than 30 beats/min above tachycardia limit
**	RUN OF 2-3 VB S	2 or 3 consecutive VBs
**	R-ON-T VB S	2 early VBs of the same shape within 15 min
**	VENTRICULAR BIGEMINY	3 VBs alternating with normal beats
**	SUPRAVENTRICULAR TACHYCARDIA	More than 3 consecutive SVBs with a rate above tachycardia limit
*	MORE THAN 5 VB S/MIN	
*	MULTIFORM VB S	2 differently shaped VBs within 5 min
*	MISSING QRS	R-R interval between normal beats at least 50% prolonged on two occasions during the past min and basic rhythm regular
*	MORE THAN 5 SVB S/MIN	
*	BRADYCARDIA	HR below bradycardia limit (normally 50/min)
*	TACHYCARDIA	HR above tachycardia limit (normally 120/min)



Table III Monitoring status alarms

Priority	Message	
**	WHAT HAS HAPPENED?	Abnormal pattern for 10 s in the absence of artefacts and no other condition applicable
**	CHECK LEADS	High level of artefacts for 30 s monitoring impossible
*	NEW QRS	New shape of reference complex rhythm unchanged
*	POISY ECG	VB detection inhibited due to artefacts for at least 15 s of last min
	CHANGE ELECTRODE PLACEMENT	Peaked W or T waves or narrow Q or S waves VB detection inhibited
	LOW AMPLITUDE	Amplitude of normal QRS < 0.3 mV VB detection inhibited
	BAD ELECTRODE CONTACT	Power line interference



Fig. 5 Status and alarm display. On the upper part of the screen are shown name HR (HPR) number of VBs (VES) during last minute and rhythm (RYTHM ORGUELB irregular) for each patient. Alarm messages appear to the right. Present display shows alarms for multiform VBs (patient 3) and more than 5 SVBs/min (FLER IN 5 SVES/MIN) from patient 7. Below is seen a trend plot from patient 3 with HR and VB frequency for the last 23 h.

Table IV Interactive procedures

---

Enter/discharge patient  
Display/change alarm limits  
Select ECG write-out mode  
Trend diagram for last 6 min/last hour/last 24 hours  
Start/stop ECG recorder  
Start/stop ECG monitoring  
Reset alarm  
Enter date and time  
Review alarm messages  
Inactivate VB monitoring  
Check alarm signals

---

### Interactive procedures

As shown in Table IV these procedures included 1 a change of alarm limits for HR trend diagrams over HR and VB frequency (Fig 8) and screening of stored alarms. Interactive routines were displayed on the lower part of the screens all showing the same picture. Thus communication with the computer except for monitoring on/off and alarm reset was only possible from one terminal at a time.

### DISCUSSION

In the development of our own system two methods for beat discrimination and classification have been used. The feature extraction method (Program II) was found to be more flexible permitting a differentiation between ventricular and supraventricular beats. The algorithm for determination of power spectrum was developed simultaneously with the feature extraction method but could have been implemented in Program I as well.

So far most CCU monitoring systems rely only on one bipolar lead. However the possible advantage of introducing two chest leads has been preliminarily tested for out-patient monitoring (Clark et al

1977 Mollé et al 1977) A few arrhythmia detectors use intracardiac or oesophageal leads in order to obtain an acceptable P wave detection (Bernard et al 1977 Lorente et al 1977 Jenkins et al 1978) Intracardiac leads impose a risk to the patients and also put extra demands on the CCU staff which explains the restricted clinical application of such systems

The sampling rate used in our program (100 Hz) is lower than that used in most other systems but has been found sufficient for arrhythmia monitoring

The monitoring system was designed for maximal flexibility with regard to the presentation of alarms and interactive communication. Thus all interactive procedures except entering the patient's name could be performed from the bedside. Most other current monitoring systems only permit full communication from the central station. The wire-less alarm system which up to now is a unique feature has been incorporated in order to enable the nurse to move around freely with little risk of overlooking an essential arrhythmia. The graded alarm function was also important to minimize interference with other nursing activities. The ranking and selection of arrhythmias in the various priority groups were made on empirical grounds. It was assumed: (1) that a highest priority alarm often required immediate action from the nurse; (2) that the second priority alarms should be recognized but usually did not require immediate action and (3) that the lowest priority alarms could be of importance but did not require active alerting. A similar philosophy for alarm grading has been described by Sanders et al (1975)

The arrhythmia write-outs have been necessary for documentation. Only one small oscilloscope in the central station was available for ECG presentation from a selected patient. The write-out with its alphanumeric printing made long term clinical evaluation of the system possible

The monitoring status alarms were introduced to aid the nurse in finding an acceptable ECG complex with a low noise content

# EVALUATION OF THE PRESENT ARRHYTHMIA DETECTOR AND MONITORING SYSTEM

## PRINCIPAL ASPECTS ON EVALUATIONAL PROBLEMS

A number of arrhythmia monitoring systems have been described in the last 10 years and in the last 2-3 years the number of commercial installations has grown rapidly. This development has taken place without documentation regarding the performance of the arrhythmia detector or the monitoring system in clinical long-term rhythm surveillance. For most systems short-term performance in selected patients has been reported but such results cannot be directly applied to long-term monitoring in the clinical setting.

All evaluation studies presented so far are based on test material collected by each investigator. The methods for evaluation may differ widely and have not always been adequately specified. In evaluating the performance of the detector it seems rational that each complex is referred to the true diagnosis. In this study as well as in most other similar investigations the results of the beat-by-beat evaluation have been expressed in the following terms:

Correct (VB) detections	$\frac{\text{No. of correct (VB) detections}}{\text{Total no. of beats (VBs)}}$
False negative (VB) detections	$\frac{\text{No. of missed or incorrect (VB) detections}}{\text{Total no. of beats (VBs)}}$
False positive (VB) detections	$\frac{\text{No. of ordinary or other ECG events classified as abnormal beats (VBs)}}{\text{Total no. of ordinary beats}}$

In the present studies various aspects of importance for the evaluation and comparison of arrhythmia detectors will be considered. Performance may differ in regular compared to irregular rhythm. The methods for beat separation and classification may work better or worse depending upon the beat configurations. The incidence of

arrhythmias may be important since a few systems suppress the detection of sporadic VBs. The characteristics of the ECG signal are extremely important and include: a) the level and type of artefacts, QRS amplitude, beat shape variations, and P and ST amplitudes in relation to the QRS. All the above factors are dependent on the ECG material and thus on the principles for ECG data collection. In addition, the reference interpretation by the cardiologist(s) is subjected to variation. The computer diagnosis should not be known to the interpreter but still classification may vary depending on the experience of the cardiologist(s) on the diagnostic criteria used and on the interpreter's knowledge of the principles for automatic classification. Two or more independent interpreters would be an advantage but could also complicate the typing of complexes when opinion differs.

From what has been said above it is obvious that the performance of the arrhythmia detector is influenced by a great number of circumstances and a proper comparison of different arrhythmia detectors would require a common ECG data base. Such a data bank has been proposed (Feldman 1974, Ripley & Arthur 1975, Zeelenberg et al 1977, Ripley & Oliver 1977), but so far no generally available ECG material has been collected.

The evaluation of a complete monitoring system in clinical routine imposes some special problems. Interaction with the system such as a change of alarm limits or criteria for arrhythmia classification will modify the results. Also a change of lead placement or signal characteristics will affect the performance. Long term evaluation during routine monitoring will be less vulnerable to a biased selection of patients provided no exclusions are made. An independent beat-by-beat interpretation of the ECG during routine use is laborious as well as the comparison between the manual and the automated interpretation. Therefore long term arrhythmia evaluation should preferably concentrate on the performance in special alarm situations. However, there is no general agreement as to the definition of various arrhythmias or as to the most relevant arrhythmias to monitor in the CCU. The performance of the system in special alarm situations can be presented principally in two ways (Holtz et al 1977). Thus the performance of the system in each type of alarm reported by the system may be analysed (cf. Fig. 10) or the performance of the system in

# EVALUATION OF THE PRESENT ARRHYTHMIA DETECTOR AND MONITORING SYSTEM

## PRINCIPAL ASPECTS ON EVALUATIONAL PROBLEMS

A number of arrhythmia monitoring systems have been described in the last 10 years and in the last 2-3 years the number of commercial installations has grown rapidly. This development has taken place without documentation regarding the performance of the arrhythmia detector or the monitoring system in clinical long-term rhythm surveillance. For most systems short-term performance in selected patients has been reported but such results cannot be directly applied to long-term monitoring in the clinical setting.

All evaluation studies presented so far are based on test material collected by each investigator. The methods for evaluation may differ widely and have not always been adequately specified. In evaluating the performance of the detector it seems rational that each complex is referred to the true diagnosis. In this study as well as in most other similar investigations the results of the beat-by-beat evaluation have been expressed in the following terms:

Correct (VB) detections	$= \frac{\text{No. of correct (VB) detections}}{\text{Total no. of beats (VBs)}}$
False negative (VB) detections	$= \frac{\text{No. of missed or incorrect (VB) detections}}{\text{Total no. of beats (VBs)}}$
False positive (VB) detections	$= \frac{\text{No. of ordinary or other ECG events classified as abnormal beats (VBs)}}{\text{Total no. of ordinary beats}}$

In the present studies various aspects of importance for the evaluation and comparison of arrhythmia detectors will be considered. Performance may differ in regular compared to irregular rhythm. The methods for beat separation and classification may work better or worse depending upon the beat configurations. The incidence of

Dr A	Dr B	classification				
		V	A	N	O	X
classification	V	I	II		III	
	A					
	N					
	O		IV		V	VI
	X					

**Fig. 9** Diagram used for the assessment of final best diagnosis and for comparison between interpretation by the computer and the physicians. After classification by the physicians (V probable VB; A possible VB; N aberrant beat probably non-VB; O ordinary beat or SVB with normal shape and I artefact) an abnormal complex or event was located to one of the 6 areas: I VB; II suspected VB; III divergent opinion between the physicians; IV abnormal non-VB; V ordinary complex (false VB); and VI artefact (false VB). VB classification by the computer was indicated in the upper left triangle of each square and computer non-VBs were marked in the lower right triangle.

**Tabl V** Comparison between classification in patients with sinus rhythm (SR) and total fibrillation (A fib). Percentage computer VBs within parentheses.

Physicians	VB		Suspected		Divergent		Abnormal		Non-Arte	
			VB		interpretation		complex		fact	
Computer	VB	Non-VB	VB	Non-VB	VB	Non-VB	VB	Non-VB	VB	Non-VB
SR	726	15	328	53	23	94	14	159	1	33
	(98)		(86)		(20)		(8)			
A fib	496	69	183	179	29	75	112	226	71	7
	(88)		(51)		(28)		(33)			

Reference to the true arrhythmia diagnosis may be studied  
(of Fig 11 12 and 13)

In some following sections monitoring in various arrhythmias will be described. Some other aspects of automated ECG monitoring will be discussed on pp 62-67

## EVALUATION OF PROGRAM I

A bipolar ECG from 15 patients with ventricular arrhythmias was recorded on tape in order to evaluate the performance of Program I. The material was also reproduced on paper at a speed of 10 mm/s and evaluated independently by two CCU physicians who had no prior knowledge of the computer diagnosis and only briefly knew the principles for arrhythmia classification used in the computer algorithms. All abnormal beats and artefacts were numbered and classified. No particular diagnostic criteria were agreed upon in advance. The final diagnosis of a complex was established with the use of a special diagram (Fig 9)

Results The duration of the recordings varied between 5 and 85 min. A total of 53 260 complexes was analysed. Out of these 2 781 or 5.2% were considered abnormal by the physicians. If all beats finally classified as definite VBs or "suspected VBs" were put together a correct classification was seen in 85% of all VBs. In individual patients the values ranged from 39 to 100%. The average number of false positive VB detections amounted to 0.45% of the total number of complexes. In individual patients the values ranged from 0.00 to 2.70%. Six of the 15 ECG recordings were from patients with atrial fibrillation. The results of the analysis in sinus rhythm (SR) and irregular rhythm were compared (Table V). The percentage of correctly classified VBs was higher in SR as compared to atrial fibrillation. The proportion of beats referred to the groups with suspected VBs divergent interpretation and abnormal non-VBs was higher in atrial fibrillation. The percentage of normal beats falsely reported as VBs in atrial fibrillation was 0.30, the corresponding figure in SR was 0.003. The most important reasons for false negative detections were absence of prematurity/compensatory pause and narrow QRS/low correla-



		classification					
		Dr B	V	A	N	O	X
classification	Dr A	V	I	II		III	
	A						
	N				IV		
	O		III			V	VI
	X					VI	VI

**Fig. 9** Diagram used for the assessment of final beat diagnosis and for comparison between interpretation by the computer and the physicians. After classification by the physicians (V probable VB & possible VB, II aberrant beat probably non-VB, III ordinary beat or SVB with normal shape, and I artefact) an abnormal complex or event was located to one of the 6 areas: I VB, II suspected VB, III divergent opinion between the physicians, IV abnormal non-VB, V ordinary complex (false VB), and VI artefact (false VB). VB classification by the computer was indicated in the upper left triangle of each square and computer non-VBs were marked in the lower right triangle.

**Table V** Comparison between classification in patients with sinus rhythms (SR) and atrial fibrillation (A fib). Percentage computer VB with parentheses.

Physians VB			Suspected		Divergent		Abnormal		For Arte-	
			VB		interp-		complex		mal fa	
Comput	VB	Non-VB	VB	Non-VB	VB	Non-VB	VB	Non-VB	VB	Non-VB
SR	726 (98)	15	328 (86)	53	23 (20)	94	14 (8)	159	1	33
A fib	496 (85)	69	183 (51)	179	29 (8)	75	112 (33)	226	71	7

tion with the prototype VB. False positive detections usually resulted from narrow ectopic beats or essentially normal beats with amplitude variations. Electrode problems or signal noise were not frequent causes of false positive VB detections.

Comments. Provided that the incidence of arrhythmias as well as the performance of the arrhythmia detector were constant during the test period it could be shown that the percentage of correctly detected VBs would fall in the interval between 82 and 90% if the total monitoring time, the total number of complexes or the total number of abnormal beats had been standardized in all test records. Average monitoring time in patients with atrial fibrillation and SR was almost identical. Three patients were also included in a set of learning ECGs used for improvement of the classification rules. The result of the arrhythmia analysis in these three patients was slightly less favourable compared to the rest. Thus the use of varying lengths of the ECG records etc probably did not introduce any bias into the results.

In the evaluation of Program I a few drawbacks of the monitoring method became apparent. The prototype VB waveform showed low correlation with bi- or tri-phasic ventricular complexes. On the other hand, in patients with a QRS interval wider than normal and particularly in left bundle branch block (BBB) the fixed VB and ordinary complexes showed a good congruence resulting in false positive VB detections. Therefore a more flexible scheme for arrhythmia analysis was developed (Program II). The coefficients in the discriminant functions used for preliminary classification of waveforms in Program II were set to obtain an optimal performance of Program II in the ECG material used in the evaluation of Program I.

#### COMPARISON BETWEEN PROGRAM I AND PROGRAM II

The relatively simple correlation technique used in Program I was compared with the more elaborate method for arrhythmia classification used in Program II (II).

A routine bipolar ECG from 12 patients with AMI was recorded on magnetic tape. The recordings were started 2-8 h after the onset of symptoms and lasted for 12 h except for one patient who died after 10

h. A paper recording of the ECG (12.5 mm/s) was scrutinized minute by minute by the author who had no knowledge of the results of the computer analysis. The manual classification was based on prematurity, QRS width, aberrancy and P wave information (if present). Only VBs were marked and in the case of difficulties in separating a possible VB from a possible SVB the beat was classified as ventricular.

The ECG material was analysed by the two computer programs and the results were presented on a 3-channel mingograph. The tracings showed the ECG, the arrhythmia diagnosis (alarm) in alphanumeric printing and a special classification code. This coding made it possible in most cases to determine the probable reasons for incorrect classification with the two programs. The performance of either program in some ventricular arrhythmias was also studied. These included VF or VT (VT four or more consecutive VBs with a rate  $>120/\text{min}$ ), two three or more than three VBs in succession, ventricular bigeminy and more than 5 VBs/min. The automated analysis was only performed once and no changes in the computer program or principles for manual interpretation were made during the study.

Usually the staff was unaware of the ECG recordings which were made in a separate room. No particular instructions were given regarding a preferable configuration of the complexes or the maximal noise-level that could be accepted. Therefore some recordings were relatively rich in artefacts and two original ECG recordings had to be omitted: one due to an unfavourable beat configuration (pointed R and T waves in combination with a low QRS amplitude) and one due to frequent noise making a proper manual interpretation impossible.

**Results.** About 50 000 ECG complexes were analysed in each patient. The total number of VBs was 2 775 and out of these 48 and 60% were detected by Program I and II respectively. The detection rate in individual patients with Program I and II ranged from 0 to 85% and from 35 to 95% respectively. Abnormal non-VBs were rarely interpreted as VBs with either program. Out of the ordinary complexes 0.06 and 0.02% were falsely classified as VBs with Program I and II respectively. Artefacts gave rise to false positive VB detections corresponding to 0.15 and 0.04% of the total number of complexes respectively. The number of correctly detected VBs

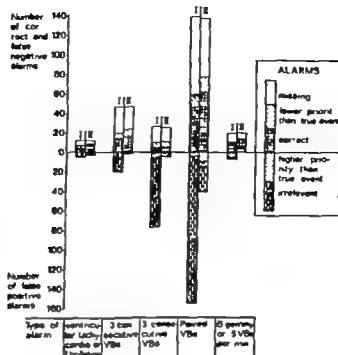


Fig. 10 Correct false positive and false negative alarms with Program I and II respectively studied with taped ECG from 12 patients

about 25% higher and false VB detection only 1/3 with Program II as compared to Program I. However, statistical analysis (sign test Documenta Geigy 1962) did not reveal any significant difference in performance between the two programs regarding false positive or false negative VB detection.

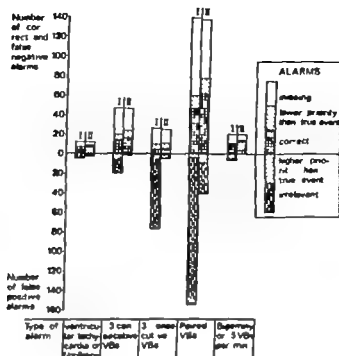
About 50% of some ventricular arrhythmias were detected with a slightly higher figure with Program II compared to Program I (Fig. 10). However, the number of irrelevant alarms (artefacts being falsely interpreted as VBs) was more than 6 times greater with Program I than with Program II. This resulted in a correct irrelevant alarm ratio corresponding to 1:3 and 3:1 with Program I and II respectively.

Table VI Probable reasons for misclassifications of VBs with Program I and II (X)

	Program I n=1452	Program II n=1095
Inhibition of the analysis due to artefacts	3	16
Inhibition due to high derivativ of VB	1	
R wave und tected due to a low amplitude	5	4
Prematurity/compensatory pause absent	17	8
Narrow QRS/low correlation with prototype VB	63	
Classified as normal beat	10	4
Classified as aberrant SVB		10
Failure of parameterization		22
VB followed by und fused complex		3
New waveform		33
Other = unknown	1	
	100	100

**Comments.** With Program II arrhythmia analysis was blocked at a lower noise level compared to Program I. Signal noise resulted in a higher proportion of missed VBs with Program II (Table VI). A majority of undetected VBs however were accompanied by a monitoring status alarm and in all these except faulty electrode contact all abnormal waveform groups were deleted automatically. As the first and sometimes also the second complex in a waveform group was unreported a high level of noise could also influence the performance in noise free portions of the ECG. Signal artefacts also increased the risks for failure of the parameterization procedure.

Abnormal groups were deleted (Program II) if no new complexes were added within a certain period of time. As the first single complex in a new group was ignored patients with a low VB frequency also showed lower figures for correct VB detection. In patients with more than 1 VB/10 min and excluding one patient with a very high noise-level 84%



**Fig. 10** Correct false positive and false negative alarms with Program I and II, respectively studied with taped ECG from 12 patients

about 25% higher and false VB detection only 1/3 with Program II as compared to Program I. However, statistical analysis (sign test Documenta Geigy 1962) did not reveal any significant difference in performance between the two programs regarding false positive or false negative VB detection.

About 50% of some ventricular arrhythmias were detected with a slightly higher figure with Program II compared to Program I (Fig. 10). However, the number of irrelevant alarms (artefacts being falsely interpreted as VBs) was more than 6 times greater with Program I than with Program II. This resulted in a correct irrelevant alarm ratio corresponding to 1.3 and 3.1 with Program I and II respectively.

Table VI Probable reasons for misclassifications of VBs with Program I and II (2)

	Program I n=1452	Program II n=1095
Inhibition of the analysis due to artefacts	3	16
Inhibition due to high derivative of VB	1	
R wave undetected due to a low amplitude		4
Prematurity/compensatory pause absent	17	8
Narrow QRS/low correlation with prototype VB	63	
Classified as normal beat	10	4
Classified as aberrant SVB		10
Failure of pairing relation		22
VB followed by undetected complex		3
New waveform		33
Other unknown	1	
	100	100

**Comments.** With Program II arrhythmia analysis was blocked at a lower noise level compared to Program I. Signal noise resulted in a higher proportion of missed VBs with Program II (Table VI). A majority of undetected VBs however were accompanied by a monitoring status alarm and in all these except faulty electrode contact all abnormal waveform groups were deleted automatically. As the first and sometimes also the second complex in a waveform group was unreported a high level of noise could also influence the performance in noise-free portions of the ECG. Signal artefacts also increased the risks for failure of the parameterization procedure.

Abnormal groups were deleted (Program II) if no new complexes were added within a certain period of time. As the first single complex in a new group was ignored patients with a low VB frequency also showed lower figures for correct VB detection. In patients with more than 1 VB/10 min and excluding one patient with a very high noise-level 84%

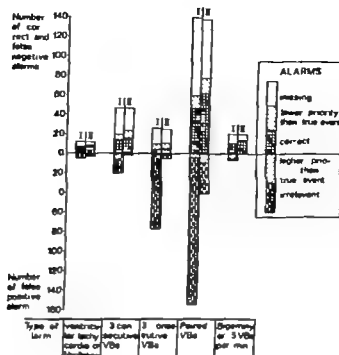


Fig. 10 Correct false positive and false negative alarms with Program I and II respectively studied with taped ECG from 12 patients

about 25% higher and false VB detection only 1/3 with Program II as compared to Program I. However statistical analysis (sign test Documenta Geigy 1962) did not reveal any significant difference in performance between the two programs regarding false positive or false negative VB detection.

About 50% of some ventricular arrhythmias were detected with a slightly higher figure with Program II compared to Program I (Fig 10). However the number of irrelevant alarms (artefacts being falsely interpreted as VBs) was more than 6 times greater with Program I than with Program II. This resulted in a correct irrelevant alarm ratio corresponding to 1:3 and 3:1 with Program I and II respectively.



punched out on paper tape which was used to summarize the results of the computer analysis. The alarm write-outs were used to establish a direct relationship between alarms and arrhythmias. The following abnormal beat categories were identified in the manual classification: premature VB (PVB), possible VB and SVB. This separation was based on prematurity, QRS aberrancy and an increase in the QRS interval. A deviation from normal in all three respects was set up as a requirement for a PVB. A deviation from normal in two resulted in a possible VB diagnosis. However narrow premature and slightly aberrant beats were classified as SVBs as well as beats of intermittent EBB type. When possible P wave information was also considered. The SVB group comprised abnormal beats not fulfilling the criteria for PVBs or possible VBs. Ordinary complexes but not abnormal ones distorted by artefacts were classified as artefacts. In the evaluation of the monitoring system the manual interpretation was used as a reference and the PVB and possible VB groups were combined to a single VB category. The highest priority alarm that should be present at ideal performance of the system was determined for each minute of monitoring. The actual alarms were compared to expected outcome at ideal performance. The result of this comparison was summarized in terms of total time for correct (C) alarms, lower (L) or higher (H) priority than expected alarms, missed or undetected (U) alarms, irrelevant (I) alarms and monitoring status alarms (A) possibly suppressing the detection of a true arrhythmia episode. The total time of each of the above categories was calculated for all arrhythmias studied with reference except for I alarms to the expected alarm and not to the actual alarm. The monitoring status alarms were only studied when these alarms possibly suppressed the detection of a true alarm. Even if a single alarm was reset in a shorter time, 4 min were always added to the total. If an alarm lasting for several minutes was reset earlier than expected, the time remaining to correct alarm reset was regarded as U. For H alarms a 4 min reset time was counted. H alarms were noted only when the reported alarm had been elicited by the true alarm event, otherwise one I and one U alarm were marked. An L alarm was noted only if the given alarm could be related to the real ECG event. In other cases a U alarm was recorded. I alarms with a lower priority than the highest priority alarm were ignored. A C alarm was not noted in U, A or L situations even if the reported alarm in itself was correct. The alarm more than 3 SVBs/min when undetected was marked as L if the

Table VII Effect of VB frequency on automated arrhythmia classification Program I-I, Program II-II

Average VB frequency	No of record-ings	True no of VBs	Correctly detected VBs			
			Total material		Mean of individual	
			(%)		Z-values	
			I	II	I	II
More than						
1 VB/10 min	5	1226	61	83	56	84
Less than						
1 VB/10 min	6	228	34	44	35	44

of all VBs were correctly classified (Table VII) . This figure must be regarded as satisfactory in view of the principles for data collection . However, even Program I performed better in patients with more frequent ventricular arrhythmias but the difference was smaller (Table VII) . A more efficient suppression of artefacts in Program II was obtained partly at the price of a lower VB detection rate in patients with a low frequency of ventricular arrhythmias

#### EVALUATION OF ARRHYTHMIA ALARMS FROM A MONITORING SYSTEM BASED ON PROGRAM II

Program II was implemented into an 8-patient monitoring system . The system was taken into routine use in 1976 and in August the same year the alarm function for all but the "R-on-T VBs and the missed QRS alarms was evaluated . The former alarm could not be studied due to difficulties in obtaining an accurate manual interpretation the latter owing to an error in the computer program

A continuous ECG recorded from all patients at a speed of 10 mm/s and analysed by the author without knowledge of the result from the computer monitoring made it possible to estimate the true incidence of arrhythmias . All alarms produced by the monitoring system were

punched out on paper tape which was used to summarize the results of the computer analysis. The alarm write-outs were used to establish a direct relationship between alarms and arrhythmias. The following abnormal beat categories were identified in the manual classification: premature VB (PVB) possible VB and SVB. This separation was based on prematurity, QRS aberrancy and an increase in the QRS interval. A deviation from normal in all three respects was set up as a requirement for a PVB. A deviation from normal in two resulted in a possible VB diagnosis. However narrow premature and slightly aberrant beats were classified as SVBs as well as beats of intermittent BBB type. When possible P wave information was also considered. The SVB group comprised abnormal beats not fulfilling the criteria for PVBs or possible VBs. Ordinary complexes but not abnormal ones distorted by artefacts were classified as artefacts. In the evaluation of the monitoring system the manual interpretation was used as a reference and the PVB and possible VB groups were combined to a single VB category. The highest priority alarm that should be present at ideal performance of the system was determined for each minute of monitoring. The actual alarms were compared to expected outcome at ideal performance. The result of this comparison was summarized in terms of total time for correct (C) alarms lower (L) or higher (H) priority than expected alarms missed or undetected (M) alarms irrelevant (I) alarms and monitoring status alarms (A) possibly suppressing the detection of a true arrhythmia episode. The total time of each of the above categories was calculated for all arrhythmias studied with reference except for I alarms to the expected alarm and not to the actual alarm. The monitoring status alarms were only studied when these alarms possibly suppressed the detection of a true alarm. Even if a single alarm was reset in a shorter time 4 min were always added to the total. If an alarm lasting for several minutes was reset earlier than expected the time remaining to correct alarm reset was regarded as H. For H alarms a 4 min reset time was counted. H alarms were noted only when the reported alarm had been elicited by the true alarm event otherwise one I and one M alarm were marked. An L alarm was noted only if the given alarm could be related to the real ECG event. In other cases a M alarm was recorded. I alarms with a lower priority than the highest priority alarm were ignored. A M alarm was not noted in M, A or L situations even if the reported alarm in itself was correct. The alarm more than 5 SVBs/min when undetected was marked as L if the

Table VII Effect of VB frequency on automated arrhythmia classification Program I-I, Program II-II

Average VB frequency	No of record-ings	True no of VBs	Correctly detected VBs			
			Total material		Mean of individual	
			(Z)		Z-values	
			I	II	I	II
More than						
1 VB/10 min	5	1226	61	83	56	84
Less than						
1 VB/10 min	6	228	34	44	35	44

of all VBs were correctly classified (Table VII) This figure must be regarded as satisfactory in view of the principles for data collection. However even Program I performed better in patients with more frequent ventricular arrhythmias but the difference was smaller (Table VII). A more efficient suppression of artefacts in Program II was obtained partly at the price of a lower VB detection rate in patients with a low frequency of ventricular arrhythmias.

#### EVALUATION OF ARRHYTHMIA ALARMS FROM A MONITORING SYSTEM BASED ON PROGRAM II

Program II was implemented into an 8-patient monitoring system. The system was taken into routine use in 1976 and in August the same year the alarm function for all but the R-on-T VBs and the missed QRS alarms was evaluated. The former alarm could not be studied due to difficulties in obtaining an accurate manual interpretation the latter owing to an error in the computer program.

A continuous ECG recorded from all patients at a speed of 10 mm/s and analysed by the author without knowledge of the result from the computer monitoring made it possible to estimate the true incidence of arrhythmias. All alarms produced by the monitoring system were

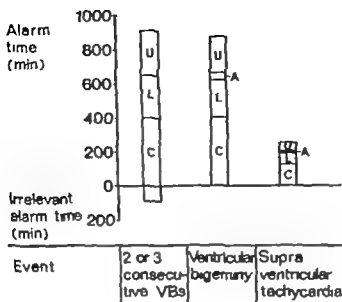
punched out on paper tape which was used to summarize the results of the computer analysis. The alarm write-outs were used to establish a direct relationship between alarms and arrhythmias. The following abnormal beat categories were identified in the manual classification: premature VB (PVB) possible VB and SVB. This separation was based on prematurity, QRS aberrancy and an increase in the QRS interval. A deviation from normal in all three respects was set up as a requirement for a PVB. A deviation from normal in two resulted in a possible VB diagnosis. However narrow premature and slightly aberrant beats were classified as SVBs as well as beats of intermittent EBB type. When possible P wave information was also considered. The SVB group comprised abnormal beats not fulfilling the criteria for PVBs or possible VBs. Ordinary complexes but not abnormal ones distorted by artefacts were classified as artefacts. In the evaluation of the monitoring system the manual interpretation was used as a reference and the PVB and possible VB groups were combined to a single VB category. The highest priority alarm that should be present at ideal performance of the system was determined for each minute of monitoring. The actual alarms were compared to expected outcome at ideal performance. The result of this comparison was summarized in terms of total time for correct (C) alarms lower (L) or higher (H) priority than expected alarms missed or undetected (U) alarms irrelevant (I) alarms and monitoring status alarms (A) possibly suppressing the detection of a true arrhythmia episode. The total time of each of the above categories was calculated for all arrhythmias studied with reference except for I alarms to the expected alarm and not to the actual alarm. The monitoring status alarms were only studied when these alarms possibly suppressed the detection of a true alarm. Even if a single alarm was reset in a shorter time 4 min were always added to the total. If an alarm lasting for several minutes was reset earlier than expected the time remaining to correct alarm reset was regarded as U. For U alarms a 4 min reset time was counted. H alarms were noted only when the reported alarm had been elicited by the true alarm event otherwise one I and one U alarm were marked. An L alarm was noted only if the given alarm could be related to the real ECG event in other cases a U alarm was recorded. I alarms with a lower priority than the highest priority alarm were ignored. A H alarm was not noted in U, A or L situations even if the reported alarm in itself was correct. The alarm more than 5 SVBs/min when undetected was marked as L if the

rhythm at the nearest 10 min print-out was marked as irregular. The alarm function in tachycardia, bradycardia and multiform VBs was only studied when such an alarm was produced by the system. Standard rate limits for the definition of various arrhythmias were used (of Table II). The alarm limits for bradycardia and tachycardia were modified whenever there was a definite change in HR outside preset limits. VB detection was inhibited at all monitoring status alarms except "faulty electrode contact". Alarms were not studied when the continuous ECG recording was interrupted.

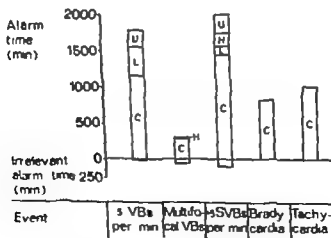
**Results** Fifty-five patients were monitored during ten 24-hour periods for a total of 1 009 h. However, about 10 h of monitoring was not available for interpretation due to short breaks in the ECG recordings. Average monitoring time in each patient was 18.0 h (0.2 - 24.0 h). A total of 5 million ECG complexes were analysed. Five of the studied alarms (asystole, VF, VT, more than 3 consecutive VBs and extreme bradycardia) occurred rarely and thus the performance in these conditions could not be properly analysed. No case with idioventricular rhythm fulfilling the definition used in the computer program was documented during the period of study. One patient with total block and an external pacemaker had short interruptions of pacemaker rhythm due to triggering problems which resulted in alarms for "more than 3 consecutive VBs" but these alarms were not otherwise considered.

Alarms for 2 or 3 consecutive VBs, ventricular bigeminy and SVT were correctly reported in 45% of expected alarm time at optimal performance (Fig. 11). I alarms amounted to about 20% of the total alarm time in these conditions but I alarms for ventricular bigeminy or SVT were rare. The performance among the lowest priority arrhythmias was better (Fig. 12): about 3/4 of alarm time was correctly indicated. A majority of L and U alarms resulted from misclassification of possible VBs. Total L and U alarm time was reduced by a factor of 0.7 if possible VBs were regarded as true SVBs when not interpreted as VBs by the computer.

Total expected alarm time ( $\Sigma$  + L + H + U + A) in top, middle and low priority arrhythmias was 0.7, 34.3 and 98.6 h respectively. Thus the total alarm time for arrhythmias was 134 h. For 70% of this time a  $\Sigma$  alarm was present for 13%.



**Fig. 11** Monitoring system performance in some arrhythmias in the second priority level C correct diagnosis U omitted or undetected event L lower priority than correct (even if within correct priority level) A monitoring status alarm present



**Fig. 12** Monitoring system performance for arrhythmias in the lowest priority level H higher priority than correct (even if within the same priority level) Other symbols as in Fig. 11

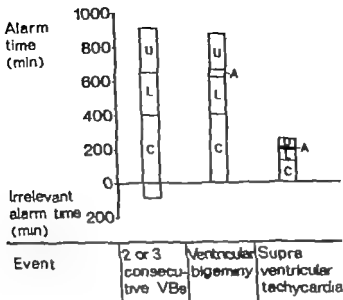
rhythm at the nearest 10 min print-out was marked as irregular. The alarm function in tachycardia, bradycardia and multiform VBs was only studied when such an alarm was produced by the system. Standard rate limits for the definition of various arrhythmias were used (of Table II). The alarm limits for bradycardia and tachycardia were modified whenever there was a definite change in HR outside preset limits. VB detection was inhibited at all monitoring status alarms except "faulty electrode contact". Alarms were not studied when the continuous ECG recording was interrupted.

**Results** Fifty-five patients were monitored during ten 24-hour periods for a total of 1 009 h. However, about 10 h of monitoring was not available for interpretation due to short breaks in the ECG recordings. Average monitoring time in each patient was 18 h (0.2 - 24 h). A total of 5 million ECG complexes were analysed. Five of the studied alarms (asystole, VF, VT, more than 3 consecutive VBs and extreme bradycardia) occurred rarely and thus the performance in these conditions could not be properly analysed. No case with idioventricular rhythm fulfilling the definition used in the computer program was documented during the period of study. One patient with total block and an external pacemaker had short interruptions of pacemaker rhythm due to triggering problems which resulted in alarms for "more than 3 consecutive VBs" but these alarms were not otherwise considered.

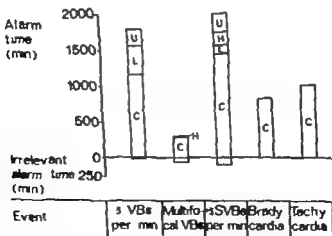
Alarms for 2 or 3 consecutive VBs, ventricular bigeminy and SVT were correctly reported in 45% of expected alarm time at optimal performance (Fig 11). I alarms amounted to about 20% of the total alarm time in these conditions but I alarms for ventricular bigeminy or SVT were rare. The performance among the lowest priority arrhythmias was better (Fig 12): about 3/4 of alarm time was correctly indicated. A majority of L and U alarms resulted from misclassification of possible VBs. Total L and U alarm time was reduced by a factor of 0.7 if possible VBs were regarded as true SVBs when not interpreted as VBs by the computer.

Total expected alarm time ( $C + L + H + U + A$ ) in top, middle and low priority arrhythmias was 0.7, 34.3 and 98.6 h respectively. Thus the total alarm time for arrhythmias was 134 h. For 70% of this time a C alarm was present for 13%.





**Fig. 11** Monitoring system performance in some arrhythmias in the second priority level C=correct diagnosis U=missed or undetected event L=lower priority than correct (even if within correct priority level) A=monitoring status alarm present



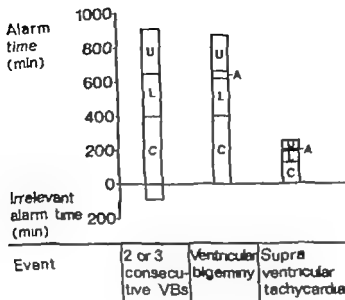
**Fig. 12** Monitoring system performance for arrhythmias in the lowest priority level H=higher priority than correct (even if within the same priority level) Other symbols as in Fig. 11

rhythm at the nearest 10 min print-out was marked as irregular. The alarm function in tachycardia, bradycardia and multiform VBs was only studied when such an alarm was produced by the system. Standard rate limits for the definition of various arrhythmias were used (cf Table II). The alarm limits for bradycardia and tachycardia were modified whenever there was a definite change in HR outside preset limits. VB detection was inhibited at all monitoring status alarms except "faulty electrode contact". Alarms were not studied when the continuous ECG recording was interrupted.

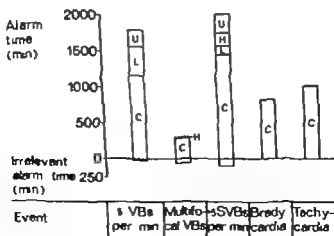
**Results** Fifty-five patients were monitored during ten 24-hour periods for a total of 1 009 h. However, about 10 h of monitoring was not available for interpretation due to short breaks in the ECG recordings. Average monitoring time in each patient was 18 h (0 - 24 h). A total of 5 million ECG complexes were analysed. Five of the studied alarms (asystole, VF, VT, more than 3 consecutive VBs and extreme bradycardia) occurred rarely and thus the performance in these conditions could not be properly analysed. No case with idioventricular rhythm fulfilling the definition used in the computer program was documented during the period of study. One patient with total block and an external pacemaker had short interruptions of pacemaker rhythm due to triggering problems which resulted in alarms for more than 3 consecutive VBs but these alarms were not otherwise considered.

Alarms for 2 or 3 consecutive VBs, ventricular bigeminy and SVT were correctly reported in 45% of expected alarm time at optimal performance (Fig 11). I alarms amounted to about 20% of the total alarm time in these conditions but I alarms for ventricular bigeminy or SVT were rare. The performance among the lowest priority arrhythmias was better (Fig 12): about 3/4 of alarm time was correctly indicated. A majority of L and H alarms resulted from misclassification of possible VBs. Total L and H alarm time was reduced by a factor of 0.7 if possible VBs were regarded as true SVBs when not interpreted as VBs by the computer.

Total expected alarm time ( $G + L + H + U + A$ ) in top, middle and low priority arrhythmias was 0.7, 34.3 and 98.6 h respectively. Thus the total alarm time for arrhythmias was 13.4 h for 70% of this time a G alarm was present for 13%.



**Fig. 11** Monitoring system performance in some arrhythmias in the second priority level C=correct diagnosis U missed or undetected event L=lower priority than correct (even if within correct priority level) A=monitoring status alarm present



**Fig. 12** Monitoring system performance for arrhythmias in the lowest priority level H higher priority than correct (even if within the same priority level) Other symbols as in Fig. 11

rhythm at the nearest 10 min print-out was marked as irregular. The alarm function in tachycardia, bradycardia and multiform VBs was only studied when such an alarm was produced by the system. Standard rate limits for the definition of various arrhythmias were used (cf Table II). The alarm limits for bradycardia and tachycardia were modified whenever there was a definite change in HR outside preset limits. VB detection was inhibited at all monitoring status alarms except "faulty electrode contact". Alarms were not studied when the continuous ECG recording was interrupted.

**Results** Fifty-five patients were monitored during ten 24-hour periods for a total of 1 009 h. However, about 10 h of monitoring was not available for interpretation due to short breaks in the ECG recordings. Average monitoring time in each patient was 18.0 h (0.2 - 24.0 h). A total of 5 million ECG complexes were analysed. Five of the studied alarms (asystole, VF, VT, more than 3 consecutive VBs and extreme bradycardia) occurred rarely and thus the performance in these conditions could not be properly analysed. No case with idioventricular rhythm fulfilling the definition used in the computer program was documented during the period of study. One patient with total block and an external pacemaker had short interruptions of pacemaker rhythm due to triggering problems which resulted in alarms for "more than 3 consecutive VBs" but these alarms were not otherwise considered.

Alarms for 2 or 3 consecutive VBs, ventricular bigeminy and SVT were correctly reported in 45% of expected alarm time at optimal performance (Fig. 11). I alarms amounted to about 20% of the total alarm time in these conditions but I alarms for ventricular bigeminy or SVT were rare. The performance among the lowest priority arrhythmias was better (Fig. 12): about 3/4 of alarm time was correctly indicated. A majority of L and H alarms resulted from misclassification of possible VBs. Total L and H alarm time was reduced by a factor of 0.7 if possible VBs were regarded as true SVBs when not interpreted as VBs by the computer.

Total expected alarm time ( $C + L + H + U + A$ ) in top, middle and low priority arrhythmias was 0.7, 34.3 and 98.6 h respectively. Thus the total alarm time for arrhythmias was 134 h. For 70% of this time a C alarm was present for 13%.

The performance of the alarm function was presented as alarm time rather than the total number of alarms of various categories. This made it possible to analyse the alarms of different priorities in situations corresponding to real-life operation of the system. Also the results in continuous arrhythmia conditions such as tachy- or bradycardia could be treated uniformly with distinct alarm events e.g. paired VEs. The performance of the system in tachy/bradycardia was excellent as evaluated from alarm time. However since these conditions usually lasted for several minutes the number of correct alarms was relatively less and probably did not contribute to an overestimation of the number of correct alarms. The average length of 2 alarms was 7.7 min compared to 4.2 min for 1 alarm which indicates that a majority of the 1 alarms occurred in isolation.

#### PERFORMANCE OF THE MONITORING SYSTEM IN ASYSTOLE VENTRICULAR FIBRILLATION AND VENTRICULAR TACHYCARDIA

In the 10-day evaluation study described in the preceding section only a few highest priority arrhythmias occurred during the period of investigation. Therefore alarm function in asystole VF and VT was investigated during 4 weeks of routine monitoring using a continuous ECG from all patients as a reference. Only the first 10 episodes of the above arrhythmias in each patient were studied. This reference ECG also contained a computer generated alphanumeric time marking which facilitated the comparison between the alarm write-outs and the manual interpretation. Thus ECG examination was performed without knowledge of the computer analysis and essentially the same criteria for the classification of heart beats were practised as in the 10-day study. However questionable abnormal beats were coded as SYBs rather than VEs.

**Fig 11g:** Sixty five patients were monitored for a total of 3 400 h. The monitoring system performance in the highest priority arrhythmias is summarized in Fig. 13.

In 5 patients a total of 24 asystole episodes were detected manually. Eight of these were accompanied by a correct alarm and two remained undetected by the automated system.

Table VIII Accuracy of arrhythmia incidence as estimated from alarm write-outs

Arrhythmia	No of patients with				Arrhythmia on write-out (%)
	verified arrhythmias	correct alarms	incorrect alarms only	missing alarms only	
2 or 3 consecutive VBs	25	16	2	7	72
Ventricular bigeminy	11	9	1	1	91
SVT	14	13	1		100
More than 5 VBs/min	18	16		2	89
More than 5 SVBs/min	14	13		1	93
(mean)					(89)
VT	19	11	4	4	79

an L alarm for 3% an H alarm for 13% a Q alarm and for 0.7% of the total time the arrhythmia occurred simultaneously with a monitoring status alarm with a higher priority. The total number of L alarms was 87 compared to 732 for Q alarms. An I alarm was present for 6.1 h. Monitoring status alarms were present for about 40 h. The alarm change electrode placement\* constituted more than 50% of this time.

By studying the performance of the monitoring system in individual patients it was possible to assess the usefulness of the monitoring system for estimation of arrhythmia incidence in a large material of CCU patients. About 90% of the patients with various ventricular and supraventricular arrhythmias were detected by the automated system (Table VIII). In a small number of patients certain arrhythmias were completely missed or incorrectly reported.

Comments. The performance of the system in multiform VBs tachy- and bradycardia was not studied in exactly the same way as the other alarms since L and H alarm time for these former conditions was not counted. It is supposed that L and H alarm time for the HR alarms was negligible. Possibly monitoring status alarms blocked some tachy-/bradycardia alarms.

The performance of the alarm function was presented as alarm time rather than the total number of alarms of various categories. This made it possible to analyse the alarms of different priorities in situations corresponding to real-life operation of the system. Also the results in continuous arrhythmia conditions such as tachy- or bradycardia could be treated uniformly with distinct alarm events e.g. paired VEs. The performance of the system in tachy /bradycardia was excellent as evaluated from alarm time. However since these conditions usually lasted for several minutes the number of correct alarms was relatively less and probably did not contribute to an overestimation of the number of correct alarms. The average length of  $\bar{c}$  alarms was 7.7 min compared to 4.2 min for  $\bar{I}$  alarms which indicates that a majority of the  $\bar{I}$  alarms occurred in isolation.

#### PERFORMANCE OF THE MONITORING SYSTEM IN ASYSTOLE VENTRICULAR FIBRILLATION AND VENTRICULAR TACHYCARDIA

In the 10-day evaluation study described in the preceding section only a few highest priority arrhythmias occurred during the period of investigation. Therefore alarm function in asystole VF and VT was investigated during 4 weeks of routine monitoring using a continuous ECG from all patients as a reference. Only the first 10 episodes of the above arrhythmias in each patient were studied. This reference ECG also contained a computer generated alphanumeric time marking which facilitated the comparison between the alarm write-outs and the manual interpretation. Thus ECG examination was performed without knowledge of the computer analysis and essentially the same criteria for the classification of heart beats were practised as in the 10-day study. However questionable abnormal beats were coded as SVBs rather than VEs.

**Results:** Sixty five patients were monitored for a total of 3 400 h. The monitoring system performance in the highest priority arrhythmias is summarized in Fig. 13.

In 5 patients a total of 24 asystole episodes were detected manually. Eight of these were accompanied by a correct alarm and two remained undetected by the automated system.

Table VIII Accuracy of arrhythmia incidence as estimated from alarm write-outs

Arrhythmia	No. of patients with				Arrhythmia on write-out (%)
	verified arrhythmias	correct alarms	incorrect alarms only	missing alarms only	
2 or 3 consecutive VBs	25	16	2	7	72
Ventricular bigeminy	11	9	1	1	91
SVT	14	13	1		100
More than 5 VBs/min	18	16		2	89
More than 5 SVBs/min	14	13		1	93
(mean)					(89)
VT	19	11	4	4	79

an L alarm for 3% an H alarm for 13% a U alarm and for 0.7% of the total time the arrhythmia occurred simultaneously with a monitoring status alarm with a higher priority. The total number of L alarms was 87 compared to 732 for U alarms. An I alarm was present for 6.1 h. Monitoring status alarms were present for about 40 h. The alarm "change electrode placement" constituted more than 50% of this time.

By studying the performance of the monitoring system in individual patients it was possible to assess the usefulness of the monitoring system for estimation of arrhythmia incidence in a large material of CCU patients. About 90% of the patients with various ventricular and supraventricular arrhythmias were detected by the automated system (Table VIII). In a small number of patients certain arrhythmias were completely missed or incorrectly reported.

Comments. The performance of the system in multiform VBs, tachy- and bradycardia, was not studied in exactly the same way as the other alarms, since L and U alarm time for these former conditions was not counted. It is supposed that L and U alarm time for the HR alarms was negligible. Possibly monitoring status alarms blocked some tachy-/bradycardia alarms.



The performance of the alarm function was presented as alarm time rather than the total number of alarms of various categories. This made it possible to analyze the alarms of different priorities in situations corresponding to real-life operation of the system. Also the results in continuous arrhythmia conditions such as tachy- or bradycardia could be treated uniformly with distinct alarm events e.g. paired VEs. The performance of the system in tachy-/bradycardia was excellent as evaluated from alarm time. However since these conditions usually lasted for several minutes the number of correct alarms was relatively less and probably did not contribute to an overestimation of the number of correct alarms. The average length of 2 alarms was 7.7 min compared to 4.2 min for 1 alarms which indicates that a majority of the 1 alarms occurred in isolation.

#### PERFORMANCE OF THE MONITORING SYSTEM IN ASYSTOLE VENTRICULAR FIBRILLATION AND VENTRICULAR TACHICARDIA

In the 10-day evaluation study described in the preceding section only a few highest priority arrhythmias occurred during the period of investigation. Therefore alarm function in asystole VF and VT was investigated during 4 weeks of routine monitoring using a continuous ECG from all patients as a reference. Only the first 10 episodes of the above arrhythmias in each patient were studied. This reference ECG also contained a computer-generated alphanumeric time marking which facilitated the comparison between the alarm write-outs and the manual interpretation. Thus ECG examination was performed without knowledge of the computer analysis and essentially the same criteria for the classification of heart beats were practiced as in the 10-day study. However questionable abnormal beats were coded as SVBs rather than VEs.

**Results:** Sixty five patients were monitored for a total of 3 400 h. The monitoring system performance in the highest priority arrhythmias is summarized in Fig. 13.

In 5 patients a total of 24 asystole episodes were detected manually. Eight of these were accompanied by a correct alarm and two remained undetected by the automated system.

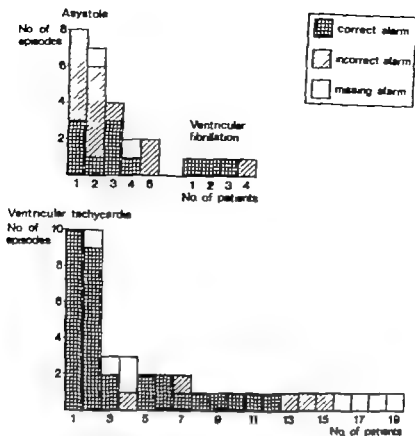


Fig. 13 Monitoring system performance in individual patients with reference to asystole VF and VT

Four VF episodes in 4 patients were found. The computer diagnosis was VF in three and VT in one patient.

Thirty-one out of 44 runs of VT were correctly detected by the monitoring system. Eight VT episodes were undetected. Two of these were preceded by artefacts which probably inhibited arrhythmia analysis. Another two were unrecognized due to inhibition of VT detection on account of an unfavourable shape of the ordinary ECG complexes. On three occasions VT was undiscovered for unknown reasons.

Time delay from the last QRS to the alarm in true asystole was less than 15 s except on two occasions when artefacts inhibited the alarm.

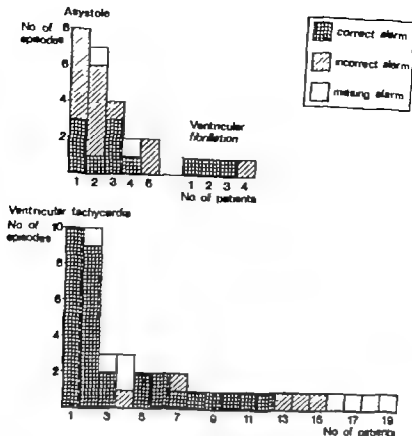
and check electrodes was reported after 40 and 60 s. The undetected asystole episodes had been preceded by alarms for VF and extreme bradycardia. Arrhythmia alarm delay in VF and in detected runs of VT ranged from 5 to 14 s and from 2 to 5 s respectively.

During the 4-week period 9 false positive asystole alarms were generated. Six of these occurred when a bedside monitor had been disconnected from the wall connector without a previous stand-by operation. The rest were caused by electrode problems and had been preceded by the message "check electrodes". The number of false positive VF and VT episodes was 13 in 3 patients and 36 in 2 patients respectively. One patient contributed 37 false positive VT alarms.

Comments. The 4-week period was not sufficiently long for a proper evaluation of the VF alarms since only 4 episodes occurred during the time period. In all these cases however a highest priority alarm was reported, indicating a high sensitivity of the system to VF. The relatively high number of misclassifications in true asystole were due either to small baseline shifts or to marked P waves in relation to the QRS in a few patients with total block. The asystole alarm was suppressed when the power of the signal exceeded a relatively low level. Therefore following this investigation threshold values in the computer program were modified in order to increase the specificity of the system to asystole. False positive asystole alarms were few and should be possible to reduce further by bedside equipment measuring the electrode impedance.

The number of false positive VF alarms was relatively high in one patient with rapid atrial fibrillation and BBB. Modifications in the program to decrease the number of false VF alarms have been suggested (Nygårds & Mølling 1977).

With the method used for studying the performance, allowing only the first 10 episodes in each patient to be included, the results will be influenced by differences in performance between patients with a small or a large number of arrhythmias. In the present investigation 53% of the first VT episodes in each patient were correctly classified. It could be calculated that about 90% of all VT episodes were correctly detected since the performance was better in patients with frequent runs of VT.



**Fig. 13** Monitoring system performance in individual patients with reference to asystole VF and VT

Four VF episodes in 4 patients were found. The computer diagnosis was VF in three and VT in one patient.

Thirty-one out of 44 runs of VT were correctly detected by the monitoring system. Eight VT episodes were undetected. Two of these were preceded by artefacts which probably inhibited arrhythmia analysis. Another two were unrecognized due to inhibition of VT detection on account of an unfavourable shape of the ordinary ECG complexes. On three occasions VT was undiscovered for unknown reasons.

Time delay from the last QRS to the alarm in true asystole was less than 15 s except on two occasions when artefacts inhibited the alarm.

VBs and non-VBs partly rested on the difference of QRS width between a reference complex and each new waveform. It is supposed that this difference on the average was less in patients with atrial fibrillation and/or BBB.

In the first two evaluations (I and II) false positive VB detection due either to misclassification of normal beats or noise with Program I was about the same even though the amount of noise differed in the two ECG materials. The extension of artefact inhibition time from 3 to 4 s might explain the above observation. VB detection rate with Program I declined markedly in the second study. There were probably several reasons for this. The diagnostic criteria used in the manual interpretation were possibly changed in such a way that some types of beats which were labelled abnormal non-VBs in the first study (I) were classified as VBs in the second study (II). This explanation might partly account for the lower rate of false positive detections (abnormal non-VBs) with Program I in the second as compared to the first evaluation study. The performance of the system in the possible VB group was markedly better with Program II than with Program I. However the factors of importance for missed VB detection with Program I were about equally distributed in the first two studies. Also irregular rhythm was more common in 15 patients rich in ventricular arrhythmias (I) than in patients with AMI (II). The difference in performance found in comprehensive evaluations of essentially the same arrhythmia detector indicates that the performance of the monitor is markedly influenced by the ECG material. It is possible that the selection of patients with AMI and a relatively short admission delay resulted in a higher than average percentage of difficult ECG records both from the point of beat shapes and signal artefacts. In the 10-d y evaluation study (III) all patients admitted to the CCU were included and the start of monitoring and the length of CCU stay in each patient were not influenced by the investigation. The selection of patients in the last evaluation (IV) was also unbiased. In this part of the study AMI was diagnosed in 25 patients and VT was detected in the write-outs in 8 of these giving a VT incidence of 32% in AMI compared to 38% during a 12-month period (VI). This indicates that other possibly important factors for system performance such as electrode care were not affected by the investigation. Also the ratio of correct to incorrect VT alarms during the 8 week and a 6-month period of

One patient with rapid atrial fibrillation and intermittent aberration contributed 36 of 37 false positive VT alarms. There does not seem to be any easy way to reduce the number of false VT alarms in such patients. In a majority of patients with atrial fibrillation and/or conduction defects no false positive VT or VF alarms were reported.

All patients with asystole or VF had at least one of these arrhythmias reproduced on the alarm write-outs as shown in Fig 13. Fifteen out of 19 patients with true VT could be recognized after scrutiny of the alarm write-outs. However VT was detected by the computer in another 3 patients: in two the continuous ECG was interrupted and in one patient VT was overlooked in the manual analysis. In 6 cases of missed VT detection the length of the arrhythmia episode was only 4 beats. Thus 3/4 of undiscovered VT episodes had the minimum length (4 beats) contrasting to 1/4 of correct VT detections. This indicates that the performance of the system was better in longer runs of VT. As most runs of VT were longer than 4 beats a more stringent definition of this alarm would probably have given a better monitoring system performance in this arrhythmia.

## DISCUSSION

The distinction between ventricular and supraventricular beats may be difficult or even impossible from a single lead recording of the ECG. This depends on a relatively common inconstancy or absence of P waves in the bipolar ECG and on difficulties in determining the true QRS axis and QRS configuration e.g. a BBB pattern. Also multiple lead ECGs are usually recorded at a higher speed which gives a better resolution and a more accurate time interval estimation e.g. QRS width. The difficulties of interpretation will result in a certain variability between different interpreters as manifested in the first study (I). Thus divergent opinions whether to refer a complex to the VB/probable VB group or not was seen in about 8% of all abnormal beats. In patients with atrial fibrillation the same figure was obtained. However the automated analysis was less accurate in this arrhythmia since rhythm criteria could not be used in irregular rhythms. Also the arrhythmia analysis in atrial fibrillation was also complicated by a greater number of abnormal waveform groups and a longer average QRS interval. In Program II the distinction between

## REVIEW OF REPORTED EVALUATIONS OF OTHER ARRHYTHMIA DETECTORS AND MONITORING SYSTEMS

As stated earlier relatively few evaluations of other arrhythmia monitors have been presented. Only a few previous beat-by-beat studies comprise more than 100 000 beats. The proportion of patients with atrial fibrillation has usually been low or unreported. Most studies presented below are comparable to the first investigation (I) regarding the size of the ECG material and the principles for ECG data collection. A comparison with the present long-term studies (III and IV) is hardly possible.

Oliver et al (1971) using the Astec-Argus algorithms and allowing adjustment of the signal amplification reported a VB detection rate of 78%. False positive VBs constituted 0.4% out of a total of around 50 000 beats. Yanowitz et al (1975) using the same principal algorithms but a simplified diagnostic scheme compared to that of the former authors reported correct detection of 90% out of 3 163 VBs and 22 false VB detections corresponding to 0.07% of all beats. However to obtain a maximal performance some of the parameters in the program were optimized in each patient. A third system based on the Astec preprocessing algorithms has been reported by Harrison et al (1974). An average of 84% of all ventricular premature beats was correctly identified with a false positive rate of 0.14%.

The accuracy of VB detection using a simple correlation technique was described in an early study by Feldman et al (1971). The material contained 48 000 beats but only 141 VBs, 100 of which were correctly classified. Twenty-two false positive VB detections were made. However only 4 out of 16 patients in the study had a significant arrhythmia. An arrhythmia detector based on the correlation technique and also on the grouping of similarly shaped beats was developed and evaluated by Shah et al (1977). The system allowed for recognition of low amplitude complexes performing an automated backward search for ectopic beats when a prolonged R-R interval was discovered. The test material comprised 146 633 beats, 5 729 labelled as ventricular and was obtained from 57 half hour records from 30 patients. The recordings were selected by a trained cardiology technician. Off-line teletyping showed a correct VB classification rate of 95%. In 2 patients with atrial fibrillation the corresponding figure was 93%. False

48  
monitoring was about the same (IV)

In the two beat-by-beat evaluations (II and III) questionable beats were diagnosed as VBs rather than SVBs. At uncertain interpretation regarding some defined arrhythmias these were classified as supraventricular rather than ventricular (IV and VI). This change in diagnostic policy during the study could have resulted in an improved performance of VT but since questionable arrhythmias were relatively rare (of VI) the overall effect of the above measure was probably small.

The manual cancelling of VB monitoring affects the monitoring system performance. During the 4-week period such an action was undertaken on two occasions but did not, however, influence the results (IV). During a 4-month period (February - May 1978) inactivation of VB recognition which left the HR and power spectrum dependent alarms unaffected took place in 9 cases out of a total around 300 in 5 patients. Intermittent pacemaker rhythm resulted in frequent false alarms for VBs in succession. In 2 patients frequent false VT alarms were seen due to an intermittent rate-dependent aberration. In one patient very frequent true VT alarms annoying the staff were observed and in another patient the nurses were much disturbed by frequent "what has happened?" alarms. During the abovementioned 4-month period 2 patients were not immediately accepted for monitoring due to a slow multifocal rhythm. In these 2 patients the manual definition of the "normal" beat was almost impossible. Thus significant monitoring problems were present in about 3% of the patients.

It was obvious that the monitoring system performance as expressed in the ratio of correct to irrelevant alarms was dependent on the alarm reset time (III). As the irrelevant alarms were usually shorter, an extension of the alarm reset time would decrease the above ratio i.e. the apparent performance would deteriorate.



## REVIEW OF REPORTED EVALUATIONS OF OTHER ARRHYTHMIA DETECTORS AND MONITORING SYSTEMS

As stated earlier relatively few evaluations of other arrhythmia monitors have been presented. Only a few previous beat by beat studies comprise more than 100 000 beats. The proportion of patients with atrial fibrillation has usually been low or unreported. Most studies presented below are comparable to the first investigation (I) regarding the size of the ECG material and the principles for ECG data collection. A comparison with the present long-term studies (III and IV) is hardly possible.

Oliver et al (1971) using the Artec Argus algorithms and allowing adjustment of the signal amplification reported a VB detection rate of 78%. False positive VBs constituted 0.4% out of a total of around 50 000 beats. Yanowitz et al (1975) using the same principal algorithms but a simplified diagnostic scheme compared to that of the former authors reported correct detection of 90% out of 3 163 VBs and 25 false VB detections corresponding to 0.07% of all beats. However to obtain a maximal performance some of the parameters in the program were optimized in each patient. A third system based on the Artec preprocessing algorithms has been reported by Harrison et al (1974). An average of 84% of all ventricular premature beats was correctly identified with a false positive rate of 0.14%.

The accuracy of VB detection using a simple correlation technique was described in an early study by Feldman et al (1971). The material contained 48 000 beats but only 141 VBs, 100 of which were correctly classified. Twenty two false positive VB detections were made. However only 4 out of 16 patients in the study had a significant arrhythmia. An arrhythmia detector based on the correlation technique and also on the grouping of similarly shaped beats was developed and evaluated by Shah et al (1977). The system allowed for recognition of low amplitude complexes performing an automated backward search for ectopic beats when a prolonged R-R interval was discovered. The test material comprised 146 633 beats, 5 729 labelled as ventricular and was obtained from 57 half hour records from 30 patients. The recordings were selected by a trained cardiology technician. Off-line testing showed a correct VB classification rate of 95%. In 2 patients with atrial fibrillation the corresponding figure was 93%. False

positive VB detection was 0.10%. Paired VBs occurred on 131 occasions. 81% correctly identified. The performance in VT (not defined) was regarded as satisfactory with correct detection of 87% of VBs belonging to this arrhythmia. Two false negative and 3 false positive VT detections were observed. The results obtained by Shah et al. were better than those reported by most earlier investigators but, surprisingly, aberrant non-VBs were absent in the ECG material.

Hultgren et al. (1975) reported the results from an evaluation study encompassing 188 276 beats. The manual classification however was not blinded and VBs and other abnormal or premature beats were not separated. In summary, 98% of all abnormal beats were detected by the system with a false positive rate of 0.10%. Quinn et al. (1975) evaluated an arrhythmia detector with 15 min records from 20 patients. Eighty-six per cent of 2 021 VBs were recognized. The false positives comprised 0.31%.

A digital arrhythmia detector permitting individual control of parameter settings was developed and evaluated by Bussman et al. (1975). In a material of 108 000 beats with nearly 10 000 VBs, 96% of the VBs and 99% of the SVBs were correctly detected.

Except for the present study only two reports concerning the performance of the alarm function during prolonged monitoring have been published so far. Vetter & Julian (1975) studied the alarms from a hybrid arrhythmia detector in 32 CCU patients. AMI was diagnosed in 22 cases. The average monitoring time on the computer in each patient was 34 h. The arrhythmia detector correctly recognized all 85 episodes of ventricular tachycardia. The true arrhythmia incidence however was obtained with the aid of the arrhythmia detector. For this purpose taped ECG material was fed into the computer and the parameter settings of the detector were modified to increase the sensitivity of the arrhythmia analysis. The prevalence of VT exceeded that of paired VBs, frequent VBs and tachy- or bradycardia. This could possibly be explained by special criteria for the definition of various arrhythmias. No specific arrhythmia diagnosis was delivered but a three-level graded sound accompanied each alarm. The total number of false positive alarms during 1 081 h of monitoring was more

In a recent study by Frost et al (1977) a computerized arrhythmia alarm system was tested during 200 hours of monitoring. The number of patients and the length of monitoring in each patient were not specified. An analog HR alarm system operated in parallel with the computer system. Using a relatively simple set of arrhythmia diagnoses and including monitoring status alarms, true alarms constituted 53 and 8% of computer-generated and analog alarms respectively. The ECG was reproduced only at an alarm and thus the number of undetected arrhythmias could not be determined. Concerning VT defined as 5 or more VBs in succession with a rate above 99, one true and 8 false positive computer alarms were reported.

Evaluation results from a 2 lead monitoring system in 306 patients showed correct detection of 91% of VBs (total 3 051) and 86% of SVBs (total 1 752). In atrial fibrillation 69% of VBs were correctly diagnosed (Bernard et al 1977).

positive VB detection was 0.10%. Paired VBs occurred on 131 occasions. 81% correctly identified. The performance in VT (not defined) was regarded as satisfactory with correct detection of 87% of VBs belonging to this arrhythmia. Two false negative and 3 false positive VT detections were observed. The results obtained by Shah et al. were better than those reported by most earlier investigators but surprisingly aberrant non-VBs were absent in the ECG material.

Hultgren et al. (1975) reported the results from an evaluation study encompassing 188 276 beats. The manual classification, however, was not blinded and VBs and other abnormal or premature beats were not separated. In summary, 98% of all abnormal beats were detected by the system with a false positive rate of 0.10%. Quinn et al. (1975) evaluated an arrhythmia detector with 15 min records from 20 patients. Eighty-six per cent of 2 021 VBs were recognized. The false positives comprised 0.31%.

A digital arrhythmia detector permitting individual control of parameter settings was developed and evaluated by Bussman et al. (1975). In a material of 108 000 beats with nearly 10 000 VBs, 96% of the VBs and 99% of the SVBs were correctly detected.

Except for the present study, only two reports concerning the performance of the alarm function during prolonged monitoring have been published so far. Vetter & Julian (1975) studied the alarms from a hybrid arrhythmia detector in 32 CCU patients. AMI was diagnosed in 22 cases. The average monitoring time on the computer in each patient was 34 h. The arrhythmia detector correctly recognized all 85 episodes of ventricular tachycardia. The true arrhythmia incidence, however, was obtained with the aid of the arrhythmia detector. For this purpose, taped ECG material was fed into the computer and the parameter settings of the detector were modified to increase the sensitivity of the arrhythmia analysis. The prevalence of VT exceeded that of paired VBs, frequent VBs and tachy- or bradycardia. This could possibly be explained by special criteria for the definition of various arrhythmias. No specific arrhythmia diagnosis was delivered but a three-level graded sound accompanied each alarm. The total number of false positive alarms during 1 081 h of monitoring was more than 300.

Table IX Definition and ranking of arrhythmias in the manual interpretation of alarm write-outs

Rank	Arrhythmia	Criteria
1	Asystole	R R interval >5 0 s
2	VF	Rapid oscillating irregular rhythm with a duration >5 0 s
3	VT	4 or more consecutive VBs with a rate >1 0/min
4	Run of VBs	3 consecutive VBs with a rate >50/min or 4 or more VBs in succession with a rate 51-120/min
5	Extreme bradycardia	HR <35/min
6	P fired VBs	
7	R-on-T VBs	This arrhythmia was only noted when the corresponding alarm had been delivered
8	Ventricular bigeminy	3 or more VBs alternating with normal beats - at least 2 of the VBs should be visible on the write-out
9	SVT	4 or more SVBs with a rate >120/min - this diagnosis required SR prior to or after the arrhythmia episode
10	More than 5 VBs/min	Alarm write-out triggered by a VB
11	More than 5 SVBs/min	Alarm write-out triggered by SVB
12	Tachycardia	SR or supraventricular rhythm with a QRS rate >120/min
13	Bradycardia	SR or supraventricular rhythm with a QRS rate <30/min

If the expected number in the four field table was 5 or less. The term significant as used below refers to a probability  $p < 0.05$  (Reference: Bailey, W. Statistical methods in biology 1951)

Results: The investigation comprised 339 patients with proven AMI and 340 patients without proven AMI

## ARRHYTHMIAS DETECTED WITH THE PRESENT MONITORING SYSTEM DURING LONG-TERM USE

The following investigation was undertaken in order to analyse arrhythmia incidence in the CCU and to investigate the prognostic importance of various arrhythmias

During 12 months 669 patients were admitted to the CCU because of a suspected myocardial infarction (MI) and monitored on the computer system (VI). Another 10 monitored patients who were admitted for other reasons but later proved to suffer from AMI were also included in the patient material. However patients with an uncertain or a long (>96 h) time delay between onset of symptoms and start of monitoring were excluded. The CCU did not receive all cardiac patients in the hospital admitted for ECG monitoring during the 12-month period. A total of 86 cardiac patients were observed in a nearby intensive care unit (ICU). Reasons for ICU admission were (1) coma persisting after resuscitation (2) imminent or overt respiratory failure and (3) all beds with automated monitoring occupied.

All write-outs produced by the monitoring system during 12 months were collected and analysed. An arrhythmia diagnosis was usually made without consideration of the diagnostic message given by the computer. However the definition and ranking of arrhythmias were essentially the same as those adopted in the computer program (Table IX). When two or more arrhythmias were present on the write-out the highest ranked condition was chosen. The HR in ordinary supraventricular or ventricular rhythms was obtained manually. The same diagnostic criteria for distinguishing between VBs and SVBs were used as described in the 4-week study (of pp 39 and 43). In each patient the length and rate of all episodes of VT were noted.

Lidocaine was usually withheld until VT or VF had been diagnosed and was given as a bolus followed by a continuous infusion for at least 12 h at a rate of 1 - 3 mg/min.

The Chi-square test (four field table two-tailed test) with Yates correction was used for the evaluation of statistical significances in relative numbers at the 5 % and 1% level. The exact test was used

Table IX Definition and ranking of arrhythmias in the manual interpretation of alarm write-outs

Ranking	Arrhythmia	Criteria
1	Asystole	R R interval $>5.0$ s
2	VF	Rapid oscillating irregular rhythm with a duration $>5.0$ s
3	VT	4 or more consecutive VBs with a rate $>120/\text{min}$
4	Run of VBs	3 consecutive VBs with a rate $>50/\text{min}$ or 4 or more VBs in succession with a rate $51-120/\text{min}$
5	Extreme bradycardia	HR $<35/\text{min}$
6	Paired VBs	
7	R-on-T VBs	This arrhythmia was only studied when the corresponding alarm had been delivered
8	Ventricular bigeminy	3 or more VBs alternating with normal beats - at least 2 of the VBs should be visible on the write-out
9	SVT	4 or more SVBs with a rate $>120/\text{min}$ - this diagnosis required SR prior to or after the arrhythmia episode
10	More than 5 VB/min	Alarm write-out triggered by a VB
11	More than 5 SVBs/min	Alarm write-out triggered by a SVB
12	Tachycardia	SR or supraventricular rhythm with a QRS rate $>120/\text{min}$
13	Bradycardia	SR or supraventricular rhythm with a QRS rate $<30/\text{min}$

If the expected number in the four field table was 5 or less. The term significant as used below refers to a probability  $p < 0.05$  (Reference: Bailey N : Statistical methods in biology 1967)

Fig 1a: The investigation comprised 339 patients with proven AMI and 340 patients without proven AMI

## ARRHYTHMIAS DETECTED WITH THE PRESENT MONITORING SYSTEM DURING LONG-TERM USE

The following investigation was undertaken in order to analyse arrhythmia incidence in the CCU and to investigate the prognostic importance of various arrhythmias

During 12 months 669 patients were admitted to the CCU because of a suspected myocardial infarction (MI) and monitored on the computer system (VI). Another 10 monitored patients who were admitted for other reasons but later proved to suffer from AMI were also included in the patient material. However patients with an uncertain or a long (>96 h) time delay between onset of symptoms and start of monitoring were excluded. The CCU did not receive all cardiac patients in the hospital admitted for ECG monitoring during the 12-month period. A total of 86 cardiac patients were observed in a nearby intensive care unit (ICU). Reasons for ICU admission were (1) coma persisting after resuscitation, (2) imminent or overt respiratory failure and (3) all beds with automated monitoring occupied.

All write-outs produced by the monitoring system during 12 months were collected and analysed. An arrhythmia diagnosis was usually made without consideration of the diagnostic message given by the computer. However the definition and ranking of arrhythmias were essentially the same as those adopted in the computer program (Table IX). When two or more arrhythmias were present on the write-out the highest ranked condition was chosen. The HR in ordinary supraventricular or ventricular rhythms was obtained manually. The same diagnostic criteria for distinguishing between VBs and SVBs were used as described in the 4-week study (of pp 39 and 43). In each patient the length and rate of all episodes of VT were noted.

Lidocaine was usually withheld until VT or VF had been diagnosed and was given as a bolus followed by a continuous infusion for at least 12 h at a rate of 1 - 3 mg/min.

The Chi-square test (four field table two-tailed test) with Yates correction was used for the evaluation of statistical significances in relative numbers at the 5% and 0.1% level. The exact test was used



Table IX Definition and ranking of arrhythmias in the manual interpretation of alarm write-outs

Ranking	Arrhythmia	Criteria
1	Asystole	R R interval > 0.5 s
2	VF	Rapid oscillating irregular rhythm with a duration > 0.5 s
3	VT	4 or more consecutive VBs with a rate > 120/min
4	Run of VBs	3 consecutive VBs with a rate > 50/min or 4 or more VBs in succession with a rate 51-120/min
5	Extreme bradycardia	HR < 35/min
6	Paired VBs	
7	R-on-T VBs	This arrhythmia was only studied when the corresponding alarm had been delivered
8	Ventricular bigeminy	3 or more VBs alternating with normal beats - at least 2 of the VBs should be visible on the write-out
9	SVT	4 or more SVBs with a rate > 120/min - this diagnosis required SE prior to or after the arrhythmia episode
10	More than 5 VBs/min	Alarm write-out triggered by a VB
11	More than 5 SVBs/min	Alarm write-out triggered by a SVB
12	Tachycardia	SE or supraventricular rhythm with a QRS rate > 120/min
13	Bradycardia	SE supraventricular rhythm with a QRS rate < 50/min

if the expected number in the four field table was 1 or less. The term significant as used below refers to a probability  $p < 0.05$  (Reference: Bailey N. Statistical methods in biology 1951)

**Results** The investigation comprised 339 patients with proven AMI and 340 patients without proven AMI

## ARRHYTHMIAS DETECTED WITH THE PRESENT MONITORING SYSTEM DURING LONG-TERM USE

The following investigation was undertaken in order to analyse arrhythmia incidence in the CCU and to investigate the prognostic importance of various arrhythmias

During 12 months 669 patients were admitted to the CCU because of a suspected myocardial infarction (MI) and monitored on the computer system (VI). Another 10 monitored patients who were admitted for other reasons but later proved to suffer from AMI were also included in the patient material. However patients with an uncertain or a long (>96 h) time delay between onset of symptoms and start of monitoring were excluded. The CCU did not receive all cardiac patients in the hospital admitted for ECG monitoring during the 12-month period. A total of 86 cardiac patients were observed in a nearby intensive care unit (ICU). Reasons for ICU admission were (1) coma persisting after resuscitation (2) imminent or overt respiratory failure and (3) all beds with automated monitoring occupied.

All write-outs produced by the monitoring system during 12 months were collected and analysed. An arrhythmia diagnosis was usually made without consideration of the diagnostic message given by the computer. However the definition and ranking of arrhythmias were essentially the same as those adopted in the computer program (Table IX). When two or more arrhythmias were present on the write-out the highest ranked condition was chosen. The HR in ordinary supraventricular or ventricular rhythms was obtained manually. The same diagnostic criteria for distinguishing between VBs and SVBs were used as described in the 4-week study (of pp 39 and 43). In each patient the length and rate of all episodes of VT were noted.

Lidocaine was usually withheld until VT or VF had been diagnosed and was given as a bolus followed by a continuous infusion for at least 12 h at a rate of 1 - 3 mg/min.

The Chi-square test (four field table two-tailed test) with Yates correction was used for the evaluation of statistical significances in relative numbers at the 5, 1 and 0.1% level. The exact test was used

Table XI CCU mortality in relation to a hythmal incident in 339 patients with proven AMI and in 340 patients without proven AMI - not significant

	CCU mortality(%) in AMI			CCU mortality(%) in non proven AMI			Diff. between AMI and non AMI patients with arrhythmia
	with	without	Diff. between	with	without	Diff. between	
	hythmia	arrhythmia		hythmia	arrhythmia		
Asystole	83	11	p<0.001	83	1	p<0.001	n.s.
VF	43	14	p<0.01	50	2	n.s.	n.s.
VT	20	13	n.s.	9	1	n.s.	n.s.
Run of VS	14	18	n.s.	2	2	n.s.	n.s.
Extreme bradycardia	61	11	p<0.001	3	2	n.s.	p<0.001
Paired VSs	13	23	p<0.03	3	2	n.s.	p<0.01
R-on-T VSs	8	17	n.s.	0	3	n.s.	n.s.
Ventricular bigeminy	13	17	n.s.	0	3	n.s.	p<0.01
SVT	10	22	p<0.01	1	3	n.s.	p<0.03
More than 5 VSs/min	18	14	n.s.	1	3	n.s.	p<0.001
More than 5 SVTs/min	16	16	n.s.	3	2	n.s.	p<0.01
Bradycardia	16	16	n.s.	4	1	n.s.	p<0.01
Tachycardia	20	11	p<0.05	6	0	p<0.01	p<0.01

Table X Arrhythmia incidence (%) in 339 patients with proven AMI and in 340 patients without proven AMI n s = not significant

	AMI	Non-AMI	Difference
Asystole	7	2	p<0.01
VF	6	2	p<0.05
VT	38	10	p<0.001
Run of VBs	50	17	p<0.001
Extreme bradycardia	11	■	n s
Paired VBs	72	38	p<0.001
R-on-T VBs	15	7	p<0.01
Ventricular bigeminy	31	20	p<0.01
SVT	50	22	p<0.001
More than 5 VBs/min	49	29	p<0.001
More than 5 SVBs/min	45	28	p<0.001
Bradycardia	39	45	n s
Tachycardia	55	34	p<0.001

All studied arrhythmias except bradycardia were significantly more common in the AMI group (Table X). Exclusion of arrhythmias occurring during the last hour in the CCU did not change this pattern even though a substantial reduction of asystole events followed after this procedure.

Overall CCU and total hospital mortality in AMI were 16 and 21% respectively. In non-AMI patients corresponding figures were 2 and 6% respectively. CCU mortality in the various arrhythmias is shown in Table XI. There were no significant differences in mortality between AMI and non-AMI patients for the following arrhythmias: asystole, VF, VT, run of VBs and R-on-T VBs. However, the absolute mortality was higher in most arrhythmias in the AMI group. When mortality was calculated after the exclusion of arrhythmias recorded in the last hour, the prognosis for patients with ventricular bigeminy and SVT also turned out to be similar in the two groups. In patients with AMI the following arrhythmias were associated with a significant increase in mortality: asystole, extreme bradycardia, VF and

XI CCU mortality in 339 patients with proven AMI and 340 patients without proven AMI

	CCU mortality in AMI		CCU mortality in non proven AMI		Difference	p
	with rhythmic arrhythmia	without rhythmic arrhythmia	with rhythmic arrhythmia	without rhythmic arrhythmia		
Asystole	83	11	83	1	p<0.001	n.s.
VF	45	14	50	8	n.s.	n.s.
VT	20	13	9	1	n.s.	n.s.
Run of VEs	14	18	2	2	n.s.	n.s.
Extreme bradycardia	61	11	5	2	n.s.	p<0.001
Delayed VEs	13	23	3	2	n.s.	p<0.01
Non-T VEs	8	17	0	3	n.s.	n.s.
Unilateral bigeminy	13	17	0	3	n.s.	p<0.01
VT	10	22	1	3	n.s.	p<0.05
More than 5 VEs/min	18	14	1	3	n.s.	p<0.001
More than 5 SVBs/min	16	16	3	2	n.s.	p<0.01
Bradycardia	16	16	4	1	n.s.	p<0.01
Chycardia	20	11	6	0	p<0.01	p<0.01

tachycardia. No prognostic conclusions regarding mortality in AMI could be made in the following arrhythmias: VT, run of VBs, R-on-T VBs, ventricular bigeminy more than 5 VBs/SVBs, and bradycardia. Patients with paired VBs and SVT had a significantly lower CCU mortality than those without these arrhythmias. This last observation, however, was not confirmed when the total hospital mortality in AMI patients with or without SVT and/or paired VBs was analysed. For all other studied arrhythmias the same prognostic information as mentioned above was obtained when total hospital instead of CCU mortality was considered.

In the non-AMI group two arrhythmias were associated with a significant increase in CCU mortality, namely asystole and tachycardia. The same applied to paired VBs when total hospital mortality was considered.

The incidence of ventricular tachycardia in AMI with the use of different definitions of this arrhythmia and mortality related to arrhythmia incidence is presented in Table XII. AMI patients with 8 or more VBs in succession at a rate  $>120/\text{min}$  had a poorer CCU and total hospital prognosis than those with no or other runs of VBs.

Comments. Total monitoring time for all 679 patients was 38 000 h. Arrhythmias in such a large material could hardly have been analysed in a continuous ECG or from a semi-automated analysis of taped ECGs.

The incidence of cardiac arrhythmias in AMI during CCU stay has been reported in a great number of publications (Spann et al 1964, Julian et al 1964, Meltzer & Kitchell 1966, Restieaux et al 1967, Lawrie et al 1967, Stock et al 1967, Lown et al 1967, Raftery et al 1969, Mogensen 1970, Henning & Lundman 1975). Patient selection, definition of arrhythmias, methods for arrhythmia documentation and principles for antiarrhythmic treatment have differed in the above studies and a comparison between the present investigation and earlier ones is difficult. The restrictive use of lidocaine possibly contributed to a relatively high incidence of ventricular tachycardia. However, the incidence of paired VBs, ventricular bigeminy, frequent VBs/SVBs, and tachy-/bradycardia certainly was higher than previously reported with conventional monitoring methods. This indicates that the automated system worked efficiently. The incidence of SVT found in the present

Table XII Incidence of ventricular tachycardia and runs of VAs in 339 patients with AMI and CCU mortality related to arrhythmia incidence n s = not significant

Criteria for

ventricular  
tachyarrhythmia

Minimum Rate length above (beats) ( $\text{min}^{-1}$ )	Incidence (%)	CCU mortality (%)		Differen s
		with arrhythmia	without arrhythmia	
3	50	65	16	n s
3	100	57	16	n s
4	120	38	13	n
4	150	23	13	$p < 0.01$
4	180	12	12	$p < 0.001$
4	210	6	14	$p < 0.001$
6	120	23	14	n
8	100	17	13	$p < 0.01$
10	100	13	13	$p < 0.001$
20	120	9	13	$p < 0.001$
40	120	8	13	$p < 0.001$

Investigation was considerably higher than the figures between 2 and 11% previously reported (Julian et al 1964 Meltzer & Kitchell 1966 Lawrie et al 1967 Jewitt et al 1967 Lowy et al 1967 Mogensen 1970) but different definitions could have partly contributed to this discrepancy

Regarding patients with nonproven infarctions arrhythmia incidence in a material of comparable size has not been reported earlier

As to the prognostic implications of various arrhythmias VT was not associated with a significantly increased mortality in AMI. This observation contrasts to earlier reports (Lawrie et al 1967 Stook et al 1967 Dalle et al 1968 Hafferty et al 1969 Mogensen 1970 Renning & Lundman 1975). It is possible that a high sensitivity of

tachycardia. No prognostic conclusions regarding mortality in AMI could be made in the following arrhythmias: VT run of VBs R-on-T VBs, ventricular bigeminy, more than 5 VBs/SVBs and bradycardia. Patients with paired VBs and SVT had a significantly lower CCU mortality than those without these arrhythmias. This last observation however was not confirmed when the total hospital mortality in AMI patients with or without SVT and/or paired VBs was analysed. For all other studied arrhythmias the same prognostic information as mentioned above was obtained when total hospital instead of CCU mortality was considered.

In the non-AMI group two arrhythmias were associated with a significant increase in CCU mortality namely asystole and tachycardia. The same applied to paired VBs when total hospital mortality was considered.

The incidence of ventricular tachycardia in AMI with the use of different definitions of this arrhythmia and mortality related to arrhythmia incidence is presented in Table XII. AMI patients with 8 or more VBs in succession at a rate  $>120/\text{min}$  had a poorer CCU and total hospital prognosis than those with no or other runs of VBs.

Comments. Total monitoring time for all 679 patients was 38 000 h. Arrhythmias in such a large material could hardly have been analysed in a continuous ECG or from a semi-automated analysis of taped ECGs.

The incidence of cardiac arrhythmias in AMI during CCU stay has been reported in a great number of publications (Spann et al 1964, Julian et al 1964, Meltzer & Kitchell 1966, Restieaux et al 1967, Lawrie et al 1967, Stook et al 1967, Lown et al 1967, Raftery et al 1969, Mogensen 1970, Renning & Lundman 1975). Patient selection, definition of arrhythmias, methods for arrhythmia documentation and principles for antiarrhythmic treatment have differed in the above studies and a comparison between the present investigation and earlier ones is difficult. The restrictive use of lidocaine possibly contributed to a relatively high incidence of ventricular tachycardia. However the incidence of paired VBs, ventricular bigeminy, frequent VBs/SVBs and tachy-/bradycardia certainly was higher than previously reported with conventional monitoring methods. This indicates that the automated system worked efficiently. The incidence of SVT found in the present



Table XII Incidence of ventricular tachycardia and runs of VEs in 39 patients with AMI and CCU mortality related to arrhythmia incidence n.s. not significant

Criteria for

ventricular

tachyarrhythmia

Minimum length (beats)	Rate above (min <sup>-1</sup> )	Incidence (%)	CCU mortality (%)		
			with arrhythmia	without arrhythmia	Difference
3	50	65	16	17	n.s.
3	100	57	16	16	n.s.
4	120	38	20	13	n
4	150	23	27	13	p<0.01
4	180	12	40	12	p<0.001
4	210	6	47	14	p<0.001
6	120	23	23	14	n
8	120	17	30	13	p<0.01
10	120	13	38	13	p<0.001
20	120	9	47	13	p<0.001
40	120	6	62	13	p<0.001

investigation was considerably higher than the figures between 2 and 11% previously reported (Julian et al 1964 Maltzer & Kitchell 1966 Lawrie et al 1967 Jewitt et al 1967 Lown et al 1967; Mogensen 1970) but different definitions could have partly contributed to this discrepancy

Regarding patients with nonproven infarctions arrhythmia incidence in a material of comparable size has not been reported earlier

As to the prognostic implications of various arrhythmias VT was not associated with a significantly increased mortality in AMI. This observation contrasts to earlier reports (Lawrie et al 1967 Stock et al 1967 Dalle et al 1968 Raftery et al 1969 Mogensen 1970 Henning & Lundman 1975). It is possible that a high sensitivity of

of the automated monitoring system to VT resulted in the detection of a great number of relatively "benign" VT episodes. Stricter criteria for the definition of ventricular tachycardia enabled us to discriminate more "malignant" arrhythmias (Table XII). Thus it is suggested that the definition of ventricular tachycardia in the computer program should be modified to include 6 VBs in succession with a rate  $>120/\text{min}$ .

The high mortality in extreme bradycardia and a high number of immediate actions by the nurses in this arrhythmia motivates transferal of the corresponding alarm to the highest priority group.

A heart rate above  $100/\text{min}$  has been considered an indication of "pump failure" in AMI (Lown et al 1967) and the more restricted definition of tachycardia used in the computer program ( $\text{HR} >120/\text{min}$ ) possibly contributed to the selection of severely diseased patients. The poorer prognosis observed in AMI and non-AMI patients with tachycardia indicates that this alarm ought to be accompanied by an alerting signal and moved to the second priority level. However in the latest version of the system an "extreme tachycardia" alarm ( $\text{HR} >150/\text{min}$ ) has been added but neither the incidence of this alarm nor its prognostic value have yet been analysed. In order to decrease the number of second priority alarms the benign character of paired VBs in AMI is sufficient evidence for assigning this alarm to the lowest priority level.

## INTERPRETATION TEST

All ECG interpretation in the 12-month investigation reported in the preceding section was done by the author and in a vast majority of the recordings only from analysis of alarm write-outs. Therefore the possible differences in interpretation between the author and a reference group was studied. This group was made up of 13 physicians. Only three arrhythmias (alarms) were selected for this testing namely VF, VT and SVT. A comparison between the interpretation by this group and by the computer was also made.

The write-outs were collected during one month (May 1977) chosen in advance by the author who collected the first probable or suspected episode of VF, VT, and SVT from each patient as well as the first (probably) false alarm regarding the above arrhythmias. Thus the test material included the first VF, VT and SVT alarm from each patient. Theoretically any patient could contribute 6 ECGs.

Each physician received an atlas (photocopy) of 61 ECG strips and was asked to code each ECG with one of the following five alternatives and in the following order of priority: (1) VF (2) VT (3) SVT; (4) artefact and (5) other. All records were analysed without clinical or other information on the patients. The computer diagnosis had been concealed in the test material. In the manual interpretation the same definitions of VF, VT and SVT as given in Table IX were used. The interpretation was made individually and the test lasted for one hour maximally. All participants were experienced in ECG interpretation and a majority had specialty competence in cardiology, clinical physiology or internal medicine but only a few had experience from the monitoring system.

Results: In Fig 13-16 the interpretation by the reference group, by the author and by the computer is compared. The ECG records were arranged to display an increasing number of positive diagnoses from left to right in the diagrams.

VF diagnoses were made by the members of the reference group in 8 ECG records. However, only in three of the cases did a majority consider VF to be present and in no case did all members of the group consider VF to be the most likely diagnosis. The computer system alone falsely

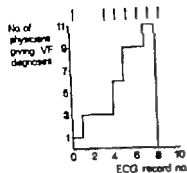
reported VF in one record with artefacts. However no true episode of VF was included in the material and this conclusion was confirmed by comparison with clinical data afterwards.

Regarding VT there was good agreement between the physicians and the author for most ECG records (Fig 15). In four instances (ECG nos 19, 20, 23 and 33 in Fig 15) a majority of the physicians and the author had divergent opinions. ECG 19 showed a run of probably ventricular beats with a rate below 120/min, ECG 20 was considered questionable by the author and therefore referred to the SVT category. ECG 23 showed SVT according to the author's opinion and ECG 33 showed a rapid regular rhythm with wide QRS complexes - a final diagnosis was made by the author after comparison with a diagnostic ECG which showed rapid supraventricular rhythm with a left BBB pattern.

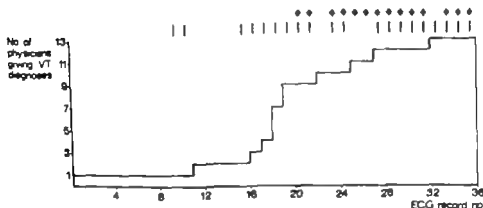
All records except one labelled SVT by a majority of the physicians were also classified as SVT by the author. The exception ECG 27 in Fig 16, showed a run of only three SVBs according to the author's interpretation. ECG 18 in Fig 16 and no 23 in Fig 15 were identical as were also several other records in Fig 14-16.

Comments The selection of ECGs for the testing was to some extent dependent on the author's classification. A number of missed and irrelevant SVT alarms were documented in the testing (Fig 16) but the principles used for ECG data collection did not permit an accurate evaluation of monitoring system performance from results in the interpretation test. Only three arrhythmias were studied. A comprehensive testing including all arrhythmias (alarms) reported by the system would require a great number of ECG strips. Such a trial was not feasible from a practical point of view. The difficulties in distinguishing VT and SVT were emphasized in the test. Also the varying opinions regarding the most likely diagnosis of the same recording were apparent. The principle for interpretation used by the author referring questionable arrhythmias to the supraventricular rather than to the ventricular category was responsible for discrepancy in interpretation in one write-out. The same principle for classification was used in the 12-month study (VI) and possibly contributed rather to an underestimation of the true number of VT episodes. The physicians' inexperience in evaluating various artefacts in the write-outs was partly responsible for their incorrect

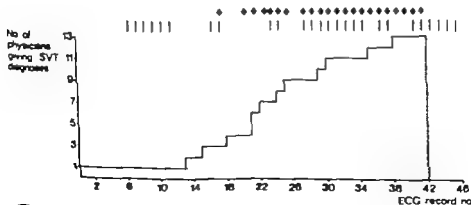
# VF diagnoses



**Fig. 14** Interpretation by 13 physicians by the author and by the monitoring system regarding VF. A positive diagnosis by the computer is indicated by a short vertical line above the diagram. No VF diagnosis was made by the author.



**Fig. 15** Interpretation by the physicians by the author and by the monitoring system regarding VT. A positive diagnosis by the author is indicated by a small square above the diagram. Other symbols as in Fig. 14.



**Fig. 16** Interpretation by the physicians by the author and by the monitoring system regarding SVT. Symbols as in Fig. 15.

## SOME OTHER ASPECTS OF AUTOMATED ARRHYTHMIA MONITORING WITH THE PRESENT SYSTEM

### Placement of electrodes and desirable configuration of ECG complexes

The accuracy of ECG monitoring with Program II was influenced by the configuration of the QRST complex. Thus the feature extraction procedure was compromised by small Q or S waves in the QRST complex. Also a pointed positive or negative T wave in relation to the QRS was undesirable and often resulted in the alarm "change electrode placement". The polarity of the signal however was irrelevant. A schematic drawing in each patient room showed desired and unfavourable configurations of the ECG complexes (Fig 17). The monitoring status alarms seem to have been more helpful than the above drawing and usually guided the nurses to an acceptable beat shape.

It is preferable to place the surface electrodes over the sternum since this position probably results in an ECG with less muscular noise compared with other thoracic lead positions. Also with a sternal position of electrodes the ECG complex is less influenced by a change in position of the patient particularly turning to his left or right side.

In all but a very low number of patients an acceptable beat configuration was obtained. Low voltage in the ECG made it impossible to get an acceptable QRS amplitude in a few patients and resulted in relatively frequent false alarms for "bradycardia" and missed QRS but after a change in threshold values in the computer program these amplitude problems have diminished markedly. A split QRS with a wide S wave sometimes observed in right BBB has been a nuisance in a few patients and resulted in repeated alarms for unfavourable electrode positions.

The 12-lead diagnostic ECG contains information regarding the beat configuration expected from various placement of chest electrodes but the nurses have not utilized this information efficiently.

Electrode artefacts could possibly be diminished by measures taken to reduce the stretching of the skin electrodes. Also some regular

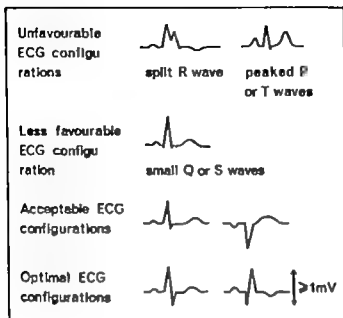


Fig. 17 Unfavourable acceptable and optimal configurations of ECG complexes (Diagram used in staff training)

testing of the electrode impedance would be advantageous but neither of these recommendations have been put into routine nor were they practised in any of the clinical evaluations previously described in this study

In summary an adequate QRS amplitude (1-2 mV) free from small Q or S waves should be sought. Smooth P or T waves with amplitudes 1/3 or less of the QRS amplitude are desirable

## SOME OTHER ASPECTS OF AUTOMATED ARRHYTHMIA MONITORING WITH THE PRESENT SYSTEM

### Placement of electrodes and desirable configuration of ECG complexes

The accuracy of ECG monitoring with Program II was influenced by the configuration of the QRST complex. Thus the feature extraction procedure was compromised by small Q or S waves in the QRST complex. Also a pointed positive or negative T wave in relation to the QRS was undesirable and often resulted in the alarm "change electrode placement". The polarity of the signal however was irrelevant. A schematic drawing in each patient room showed desired and unfavourable configurations of the ECG complexes (Fig 17). The monitoring status alarms seem to have been more helpful than the above drawing and usually guided the nurses to an acceptable beat shape.

It is preferable to place the surface electrodes over the sternum since this position probably results in an ECG with less muscular noise compared with other thoracic lead positions. Also with a sternal position of electrodes the ECG complex is less influenced by a change in position of the patient particularly turning to his left or right side.

In all but a very low number of patients an acceptable beat configuration was obtained. Low voltage in the ECG made it impossible to get an acceptable QRS amplitude in a few patients and resulted in relatively frequent false alarms for bradycardia and "missed QRS", but after a change in threshold values in the computer program these amplitude problems have diminished markedly. A split QRS with a wide S wave sometimes observed in right BBB has been a nuisance in a few patients and resulted in repeated alarms for unfavourable electrode positions.

The 12-lead diagnostic ECG contains information regarding the beat configuration expected from various placement of chest electrodes but the nurses have not utilized this information efficiently.

Electrode artefacts could possibly be diminished by measures taken to reduce the stretching of the skin electrodes. Also some regular



Other previously described methods for the reduction of false positive VF alarms should be implemented (Nygårds & Ruiting 1977). A special procedure for the detection of low amplitude ectopic beats would be advantageous. The ranking and priorities of some arrhythmia alarms should be changed in the way described on page 58. A special alarm should be given if the automated monitoring is interrupted.

#### Education of personnel

All education regarding the handling of interactive procedures, the use of monitoring on/off and alarm reset keys etc. has been easy. All new nurses were trained by their colleagues. The time needed for an inexperienced person to learn how to operate the system and how to use the interactive programs has been less than half an hour in most cases. The care of electrodes and their optimal placement, however, needs continuous attention and education from the staff physician.

A schedule in the nurses station showed all the alarms and their priorities. The codes of all interactive programs were listed on the video screen. This information was not available in the patient rooms.

#### ECG monitoring in patients with external pacemakers and with other special rhythms

Intermittent external pacemaker activity has usually resulted in false alarms for VEs in succession. A high frequency of such alarms has been annoying to the staff. In these situations the VE detecting function has been turned off and the rate limits narrowed so that a dropped beat or the resumption of normal rhythm would be recognized from RR criteria only. These actions usually worked satisfactorily. A pacemaker rhythm overridden e.g. by SR with a narrow QRS complex resulted in the alarm new QRS after about 2 min. The pacemaker pulse was usually undetected but on rare occasions it was sampled explaining a few alarms for check electrodes in pacemaker patients.

The presence of continuous VT at the start of monitoring has usually been interpreted as tachycardia by the computer system. Even for the human observer the distinction between VT on admission and a rapid rhythm with BBB is often impossible from the bipolar ECG. In such

## Starting monitoring

After the attachment of skin electrodes and the connection of patient cables to the bedside unit monitoring is started by pressing a special key on the unit. After 15-45 s monitoring starts and HR will be indicated on the video screen. If the ECG signal is unsatisfactory the message "check ECG signal" will be displayed.

Monitoring for a selected patient may be initiated or terminated in any patient room or in the central station.

## Technical problems

The technical problems have been few after the introduction of the computerized monitoring system in clinical routine. Overheating of the computer as a result of insufficient ventilation has occurred twice. The keyboard of the video screen as well as the ink-jet pens of the Mingograph have been exchanged. On a few occasions monitoring has stopped for unknown reasons. In these cases the system has been restarted within seconds or minutes from the computer room by pressing a special key.

## Modifications in the computer program

All computer algorithms had been thoroughly tested before the system was taken into routine use in 1976. However, since the introduction a few changes in the program have been necessary. Some of these modifications have been mentioned earlier. The lowest acceptable QRS amplitude was decreased from about 0.6 to 0.3 mV at the patient electrodes. The asystole alarm was shown to be inhibited by moderate base line shifts or marked P waves and these findings made it necessary to change some threshold values. The program has also been modified in order to accept patients with a very low HR - in the first version of the program 5 or more ECG complexes should be recorded within 10 s before a reference complex was approved. The alarm "extreme tachycardia" was added in 1977. Future improvements of the system should include a special subroutine for pacemaker patients and some circuits in the bedside equipment for measuring electrode impedance. This last method would probably result in improved electrode care with a decrease in the number of irrelevant alarms.

not cause any harm to the patients. Lidocaine was given to 21% of 339 AMI patients. VT and VF had been diagnosed in 70% and 24% of these patients respectively.

In several patients without suspected AMI admitted for arrhythmia monitoring, slow or fast (symptomatic) arrhythmias were documented and the need for tape recordings of the ECG was obviated. In this patient category a telemetry signal fed into the computer could accomplish monitoring in the ambulatory patient.

#### Nurses' opinion on the system

The nurses' opinion on the automated system was studied in December 1976. Thirteen nurses participated and all considered that working conditions in the CCU had improved since the introduction of the automated monitoring system. However, one nurse also thought that the high number of arrhythmias detected had a negative effect by increasing demands on the staff. Five out of 10 nurses thought that patient care had improved with the system and the rest considered it unchanged. Eight out of 11 considered the ratio of false to true alarms of all kinds acceptable or low, whereas three thought this ratio too high.

Moderately frequent false highest priority alarms (1.5 per hour for some hours) in a few patients per month have been accepted by the nurses.

cases the "true" diagnosis was obtained from the case records or the ECGs recorded on admission

The frequency of highest priority alarms in a few patients with frequent episodes of VT has been disturbing. Cancellation of VB monitoring has still resulted in VT alarms generated from the power spectrum analysis or from outstepping HR limits. During a 28-month period true VF has occurred in two patients without a correct alarm being given. In one of these patients with cardiogenic shock a slow frequency VF occurred terminally and was accompanied by the alarm "check electrodes". In the other "what has happened?" was reported due to VF with a low amplitude. About 100 VF episodes have been correctly classified during a 2 1/2-year period.

#### Effects on arrhythmia documentation and patient care

The write-outs have been invaluable for arrhythmia documentation. However, on account of the present study all alarm write-outs were collected and could not be added to the case records. In the present version of the system no hard copy report has been obtainable. However, a special subroutine made it possible to punch out HR, VB frequency and reported alarms for each patient and this feature was utilized in the second evaluation study (II).

Regarding the effect of automated monitoring on patient care it is not possible to say that the prognosis has been improved since the introduction of the system. However, compared to the ratemeter system previously relied on in the CCU, a marked improvement in the quality of ECG monitoring has been brought about with the automated system. In view of results from 24 h visual ECG monitoring in other CCUs, the high incidence of various arrhythmias found in our CCU (Table X) indicates a high efficiency of the automated monitoring system. Thus, constant human ECG monitoring does not seem to be necessary with efficient use of the system.

Although single episodes of VT were considered an indication for antiarrhythmic treatment in patients with a suspected or a proven AMI, several patients with paroxysmal VT of short length did not receive lidocaine by infusion. As evaluated from the prognosis in ventricular tachycardia reported in Table XII, this restrictive use of the drug did

supraventricular tachycardia (SVT) The lowest priority arrhythmia alarms comprised more than 5 VB/SVBs per min missed QRS bradycardia (HR <50/min) and tachycardia (HR >120/min) Also a number of monitoring status alarms were included in the system

The alarm function during 1 000 h of monitoring (5 million ECG complexes) was evaluated in 55 CCU patients The total alarm time at optimal performance was determined to 134 h for 70% of this time a correct alarm and for 17% an incorrect alarm was present 13% of alarm time was unreported Monitoring status alarms and irrelevant alarms were present for 46 and 6 h respectively In a 4 week study comprising 3 000 monitoring hours also analyzed manually the computer correctly diagnosed 8 out of 24 asystole events 3 out of 4 VF and 31 out of 44 VT episodes Only a few of these arrhythmias were unreported

Several factors influencing the accuracy of the automated arrhythmia analysis have been found The characteristics of the ECG material are of great importance for the performance Negative factors include an irregular basic rhythm the presence of conduction disturbance variability in shapes of normal and ectopic beats and a high noise level Patients with intermittent external pacemaker activity or rate-dependent conduction disturbances produced frequent false alarms These patients comprised about 2% of the total

The alarm write-outs generated by the monitoring system (Program II) contained the arrhythmias from about 90% of the patients with various ventricular and supraventricular rhythms Therefore arrhythmia incidence and prognosis in various arrhythmias were studied during long term use of the system An investigation was performed in 339 patients with proven AMI and in 340 patients without proven AMI All arrhythmias except bradycardia were significantly more common in the AMI group VF and SVT were observed in 38 and 50% of AMI patients respectively In the non-AMI group the corresponding figures were 10 and 22% respectively The mortality in the following arrhythmias was not significantly different between AMI and non-AMI patients asystole VF VT consecutive VBs and R-on-T VBs In AMI the following arrhythmias were associated with a significant increase in mortality: asystole VF extreme bradycardia and tachycardia In the non-AMI group asystole paired VBs and tachycardia were associated

## SUMMARY

A multipatient monitoring system for arrhythmia detection in the CCU has been developed and evaluated

In the first arrhythmia detector (Program I) ventricular ectopic beats (VBs) were recognized by correlation with a stored fixed VB waveform. In a set of test ECGs (50 000 complexes) 94% of true VBs were recognized in sinus rhythm compared to 74% in atrial fibrillation.

In the second arrhythmia detector (Program II) a more sophisticated method for beat separation and classification was developed. QRST classification was based on a feature extraction scheme utilizing four approximately orthonormal basis functions. The waveform of each beat was classified with the aid of two discriminant functions operating on the waveform features of each beat and on rhythm data. Similar beats were clustered. The classification of ventricular fibrillation (VF), ventricular tachycardia (VT) and asystole was partly based on the power spectrum of the ECG.

Program I and II were compared in a beat-by-beat study using taped ECG recordings (about 600 000 beats) from 12 patients with acute myocardial infarction (AMI). Program I and II correctly detected 48 and 60% of all VBs respectively. Irrelevant VB detections usually caused by noise corresponded to 0.21 and 0.07% of all beats respectively. In some special ventricular arrhythmias (alarms) the ratio of correct irrelevant alarms was 1:3 with Program I and 3:1 with Program II.

Program II was implemented in an 8-patient monitoring system taken into routine use in 1976. Communication with the system could be performed at bedside as well as at the nurses station. At an alarm a delayed ECG and an arrhythmia diagnosis were presented on a write-out. A wireless alarm transmitting system alerted the nurses through small pocket receivers. All alarms were grouped into three priority levels. The highest level included alarms for asystole, VF and VT. The second level included alarms for runs of VBs, extreme bradycardia (heart rate (HR) < 35/min), extreme tachycardia (HR > 150/min), idioventricular rhythm, paired VBs, R-on-T VBs, ventricular bigeminy and

supraventricular tachycardia (SVT). The lowest priority arrhythmia alarms comprised more than 5 VB/SVBs per min missed QRS bradycardia (HR <50/min) and tachycardia (HR >120/min). Also a number of monitoring status alarms were included in the system.

The alarm function during 1 000 h of monitoring (5 million ECG complexes) was evaluated in 55 CCU patients. The total alarm time at optimal performance was determined to 13% H for 70% of this time a correct alarm and for 17% an incorrect alarm was present. 13% of alarm time was unreported. Monitoring status alarms and irrelevant alarms were present for 46 and 6 H respectively. In a 4-week study comprising 3 000 monitoring hours also analyzed manually the computer correctly diagnosed 8 out of 24 asystole events, 3 out of 4 VF and 31 out of 44 VT episodes. Only a few of these arrhythmias were unreported.

Several factors influencing the accuracy of the automated arrhythmia analysis have been found. The characteristics of the ECG material are of great importance for the performance. Negative factors include an irregular basic rhythm, the presence of conduction disturbance, variability in shapes of normal and ectopic beats and a high noise level. Patients with intermittent external pacemaker activity or rate-dependent conduction disturbances produced frequent false alarms. These patients comprised about 2% of the total.

The alarm write-outs generated by the monitoring system (Program II) contained the arrhythmias from about 90% of the patients with various ventricular and supraventricular rhythms. Therefore arrhythmia incidence and prognosis in various arrhythmias were studied during long term use of the system. An investigation was performed in 339 patients with proven AMI and in 340 patients without proven AMI. All arrhythmias except bradycardia were significantly more common in the AMI group. VT and SVT were observed in 38 and 50% of AMI patients respectively. In the non-AMI group the corresponding figures were 10 and 22% respectively. The mortality in the following arrhythmias was not significantly different between AMI and non-AMI patients: asystole, VF, VT, consecutive VBs and R-on-T VBs. In AMI the following arrhythmias were associated with a significant increase in mortality: asystole, VF, extreme bradycardia and tachycardia. In the non-AMI group asystole, paired VBs and tachycardia were associated





## ACKNOWLEDGEMENTS

I wish to express my sincere gratitude to all who have helped me during the study and specially to acknowledge:

The former Head of Medical Department I Södersjukhuset the late Gösta von Reis M D for his positive attitude and support  
Georg Matell M D present Head of the Department and Professor Ove Wigertz Ph D Head of the Department of Medical Informatics Linköping University who together initiated and led the research project resulting in the present monitoring system They have followed the present study with great interest and supported me generously

Kata-Erik Nygård M Sc who developed and implemented the methods for automated arrhythmia monitoring My close cooperation with him during many years has been an invaluable experience

Sture Bovegård M D who reviewed all manuscripts and provided valuable help and criticism

Oscar Rosenbaser M D for stimulating discussions regarding the clinical parts of the study

Peter Blomqvist M Sc for programming work and assistance

Bena-Olor Malmund M D for organizing the work within the clinic in an efficient way

Mrs Birgitta Gæmner laboratory engineer for her never failing helpfulness She also prepared all figures

Miss Barbro Hulting and Mrs Britt Axelsson who skilfully typed the manuscripts

Johan Lagerfelt M D who kindly reviewed the English

Rolf Bergin M D who put the facilities of the Computer Department at the Karolinska Institute at my disposal

All colleagues who participated in the interpretation test as well as the nurses who took part in the inquiry

All members of the staff in the CCU headed by Mrs Kerstin Wijk Their work was essential for the collecting of ECG records and clinical data

Economical support was obtained from the Swedish Board for Technical Development (STU) and the Stockholm County Council

with a significant increase in mortality AMI patients with paired VBs and/or SVT had a significantly better prognosis in the CCU than those without these arrhythmias AMI patients with 8 or more VBs in succession with a rate  $>120/\text{min}$  had a poorer CCU and total hospital prognosis than those with no or other runs of VBs Based on the above findings changes in the definitions and priorities of some alarms are suggested

The high incidence of arrhythmias observed in the CCU was probably mainly the result of a high quality of arrhythmia monitoring Constant human ECG monitoring does not seem to be necessary with efficient use of the present system Few technical problems have been encountered during a 2-year period This fact, in combination with a low frequency of false alarms, has contributed to a positive attitude of the nurses towards the system

- cular tachycardia *Acta Cardiol* 22:519 1968
- Day H W An intensive coronary care area *Dis Chest* 44 423  
1963
- DeJongh R Bloek P & Butter A : Tachyarrhythmias in  
myocardial infarction *Circulation* 45:681 1972
- Documenta Geigy Scientific Tables Geigy S A Basle 1962
- Feyer M D Wallace A G & Stacy H W : A real-time waveform  
analyzer for detection of ventricular premature beats  
*J Appl Physiol* 29 541 1970
- Feldman C L Amazeen P G Klein M D & Lown B : Computer  
detection of ventricular ectopic beats *Comp Biomed Res*  
3:666 1971
- Feldman C L : Evaluation of arrhythmia detectors *Computers  
in Cardiology* p 21 IEEE Computer Society 1974
- Fenton P Fitton H Hampton J Hayward R & Willmott W :  
A method for counting ectopic beats by computer analysis of  
R-R intervals *Europ J Cardiol* 5:29 1977
- Fordard H Computer handling of coronary care unit data  
*Med Clin North Am* 57:143 1973
- Frost D Yanowitz F & Pryor A Evaluation of a computerized  
arrhythmia alarm system *Am J Cardiol* 39:583 1977
- Eber E Automatic detection and recording of cardiac arrhyth-  
mias *JAMA* 170:1782 1959
- Eggenbeijer F Glaser B Zaalenberg C Ritsma van Eek H  
& Engenholtz P G Databank for arrhythmia detection programs  
*Trends in Computer-Processed Electrocardiograms* p 91 North-  
Holland Publishing Company 1977
- Harrison D C Sanders W J Buckley H T & Alderman E L :  
Development and validation of a coronary care unit monitoring  
system *Proc First World Congress on Intensive Care* p 21  
London 1974
- Herming R & Lundman T Swedish co-operative CCU study  
*Acta Med Scand (Suppl)* 586 1975
- Korveendahl S : Influence of treatment in a coronary care unit  
on prognosis in acute myocardial infarction *Acta Med Scand*  
(Suppl) 519 1971
- Holmberg S Rydén L & Waldenström A Efficiency of arrhyth-  
mia detection by nurses in a coronary care unit using a de-  
centralized monitoring system *Br Heart J* 39:1019 1977
- Kultgren H Shettigar U & Specht D Clinical evaluation

# REFERENCES

- Bailey N Statistical methods in biology The English Universities Press Ltd London, 1961
- Bashour, P A , Jones E & Edmonson, R Cardiac arrhythmias in acute myocardial infarction II Incidence of the common arrhythmias with special reference to ventricular tachycardia Dis Chest 51 520 1967
- Bazett H C An analysis of the time relationship in electrocardiograms Heart 7 353 1920
- Bernard R , Sajet, M Demeester, M , Wainzel, H & Rey W Experience with 2 lead monitoring system Advantages-disadvantages-evolution Trends in Computer-Processed Electrocardiograms, p 65 North-Holland Publishing Company, 1977
- Breithardt, G Gleichmann D Loogen F & Seipel L Heutiger Stand und Probleme der Computeranalyse von Extrasystolen Med Technik 93 114 1973
- Breithardt G , Loogen F Schmiel F K & Seipel L A new method for automated detection of the R-on-T phenomenon Am Heart J 89 759 1975
- Brown K W G MacMillan R L Forbath N Mel grano F & Scott J W Coronary unit An intensive-care centre for acute myocardial infarction Lancet 2 349 1963
- Bussman W -D Voswinckel W Ameling W & Effert S Online analysis of e s g arrhythmias with a digital computer Med Biol Eng 13 382 1975
- Cannon, D & Harrison D C Detection of ventricular arrhythmias in real-time with a portable analog computer Am J Cardiol 33 399 1974
- Christiansen I Iversen E & Skouby A P Benefits obtained by the introduction of a coronary-care unit A comparative study Acta Med Scand 189 285 1971
- Clark K Hitchens R Ritter A Ranking S Oliver G C & Thomas L Argus/2H A dual-channel Holter-tape analysis system Computers in Cardiology p 191 IEEE Computer Society 1977
- Cox J R Nolle F M Foxzard H A & Oliver G C AZTEC a preprocessing program for real-time ECG rhythm analysis IEEE Trans Biomed Eng 15 128 1968
- Dalle X S Meltzer E & Kravitz B A new look at ventri-

- ocular tachycardia *Acta Cardiol* 22:519 1968
- Day H V : An intensive coronary care area *Dis Chest* 44 423  
1963
- Deanotis R Block P & Hutter A Tachyarrhythmias in  
myocardial infarction *Circulation* 45:681 1972
- Documenta Geigy Scientific Tables Geigy S A Basle 1962
- Feezor M D Wallace A B & Stacy R W A real-time waveform  
analyzer for detection of ventricular premature beats  
*J Appl Physiol* 29:541 1970
- Feldman C L Anaxeen P G Klein M D & Lown B : Computer  
detection of ventricular ectopic beats *Comp Biomed Res*  
3:666 1971
- Feldman C L Evaluation of arrhythmia detectors Computers  
in Cardiology p 21 IEEE Computer Society 1974
- Fenton P Fitton D Hampton J Hayward R & Willmott W :  
A method for counting ectopic beats by computer analysis of  
R-R intervals *Europ J Cardiol* 5 29 1977
- Fossard H Computer handling of coronary care unit data  
*Med Clin North Am* 57 143 1973
- Frost D Yanowitz F & Pryor A : Evaluation of a computerized  
arrhythmia alarm system *Am J Cardiol* 39:583 1977
- Haber E : Automatic detection and recording of cardiac arrhyth-  
mias *JAMA* 170:1782 1959
- Hagenheijer F Glaser B Zeelenberg C Ritsers van Eek H  
& Hugenholz P G Databank for arrhythmia detection programs  
*Trends in Computer Processed Electrocardiograms* p 91 North-  
Holland Publishing Company 1977
- Harrison D C Sanders W J Buckley H T & Alderman E L :  
Development and validation of a coronary care unit monitoring  
system *Proc Fir t World Congress on Intensive Care* p 21  
London 1974
- Henning B & Lundman T : Swedish co-operative CCU study  
*Acta Med Scand (Suppl)* 386 1975
- Hofvrend Hl S : Influence of treatment in a coronary care unit  
on prognosis in acute myocardial infarction *Acta Med Scand*  
(Suppl) 519 1971
- Holmberg S Rydén L & Waldenström A : Efficiency of arrhyth-  
mia detection by nurses in a coronary care unit using a de-  
centralised monitoring system *Br Heart J* 39:1019 1977
- Multgren H Shettigar U & Specht D Clinical evaluation

## REFERENCES

- Bailey, N Statistical methods in biology The English Universities Press Ltd, London 1961
- Bashour F A Jones E & Edmonson R Cardio arrhythmias in acute myocardial infarction II Incidence of the common arrhythmias with special reference to ventricular tachycardia Dis Chest 51 520 1967
- Bazett H C An analysis of the time relationship in electrocardiograms Heart 7 353 1920
- Bernard R , Sajat M Demeester M Wainzel, H & Rey W Experience with 2 lead monitoring system Advantages-disadvantages-evolution Trends in Computer-Processed Electrocardiograms, p 65 North-Holland Publishing Company, 1977
- Breithardt, O Gleichmann, U , Loogen F & Seipel L Heutiger Stand und Probleme der Computeranalyse von Extrasystolen Med Technik 93 114 1973
- Breithardt G , Loogen F Schmiel F K & Seipel L A new method for automated detection of the R-on-T phenomenon Am Heart J 89 759, 1975
- Brown, K W G MacMillan R L Forbath N Melgrano F & Scott J W Coronary unit An intensive-care centre for acute myocardial infarction Lancet 2 349 1963
- Bussman W -D Voswinckel W Ameling W & Effert S Online analysis of e s g arrhythmias with a digital computer Med Biol Eng 13 382 1975
- Cannon D & Harrison D C Detection of ventricular arrhythmias in real-time with a portable analog computer Am J Cardiol 33 399 1974
- Christiansen I Iversen K & Skouby A P Benefits obtained by the introduction of a coronary-care unit A comparative study Acta Med Scand 189 285 1971
- Clark K Hitchens R Ritter A Ranking S Oliver G C & Thomas L Argus/2H A dual-channel Holter-tape analysis system Computers in Cardiology p 191 IEEE Computer Society 1977
- Cox J R Welle F M Foxzard H A & Oliver G C AZTEC a preprocessing program for real-time ECG rhythm analysis IEEE Trans Biomed Eng 15 128 1968
- Dalle I S Meltzer E & Kravitz B A new look at ventri-

- Lorente P, Henzel D, Hardou A, Lesigne C & Levy B : A hardware device for recognition of P and QRS waves. *Med Progr Technol* 4:177 1977
- Lown B, Amarasingham R & Neumann J : New method for terminating cardiac arrhythmias. Use of synchronized capacitor discharge. *JAMA* 182:548 1962
- Lown B, Vassaux C, Hood W, Fakhro A, Kaplinsky E & Sobergo G : Unresolved problems in coronary care. *Am J Cardiol* 20:494 1967
- Lown B, Klein M & Hershberg P : Coronary and pre-coronary care. *Am J Med* 46:705 1969
- MacMillan R L, Brown K W G, Peckham G B, Kahn O, Hutchinson D B & Paton M : Changing perspectives in coronary care. A five year study. *Am J Cardiol* 20:451 1967
- Meltzer L E & Kitchell J B : The incidence of arrhythmias associated with acute myocardial infarction. *Progr Cardiovasc Dis* 9:50 1966
- Mogensen L : Ventricular tachyarrhythmias and lignocaine prophylaxis in acute myocardial infarction. A clinical and therapeutic study. *Acta Med Scand (suppl)* 513 1970
- Neher H, Popiliev I, Astardjian G, Radev C & Galinov C : Quantitative characterization of heart rhythm disturbances by means of Andros-R, a logical rhythm analyser. *Jap Heart J* 12:573 1971
- Nelson J M : An adaptive arrhythmia monitor. *Computers in Cardiology* p 211. IEEE Computer Society 1974
- Nolle P M : The Argus monitoring system. A reappraisal. *Trends in Computer Processed Electrocardiograms* p 11. North-Holland Publishing Company 1977
- Nygårds M E, Blomqvist P, Hulting J, Matell G & Wigertz G : Classification of QRS complexes based on a dedicated scheme for feature extraction. *Computers in Cardiology* p 193. IEEE Computer Society 1975
- Nygårds M E & Hulting J : Recognition of ventricular fibrillation utilizing the power spectrum of the ECG. *Computers in Cardiology* p 393. IEEE Computer Society 1977
- Oliver G C, Nolle P M, Wolf G A, Cox J R & Ambon H D : Detection of premature ventricular contractions with a clinical system for monitoring electrocardiographic rhythms. *Comp Biomed Res* 4:523 1971

- of a new computerized arrhythmia monitoring system *Heart Lung* 4 241, 1975
- Hulting J Nygård M-E & Wigertz, O : Problems in the evaluation of arrhythmia monitoring systems *Trends in Computer-Processed Electrocardiograms* p 75 North-Holland Publishing Company 1977
- Jenkins J Wu D & Arzbacher R Computer diagnosis of abnormal cardiac rhythms employing a new P-wave detector for interval measurement *Comp Biomed Res* 11 17, 1978
- Jewitt M, Balcon, R Raftery, E R & Oram, S Incidence and management of supraventricular arrhythmias after acute myocardial infarction *Lancet* 2 734 1967
- Julian, D G Valentine, P A & Miller, G G Disturbances of rate rhythm and conduction in acute myocardial infarction A prospective study of 100 consecutive unselected patients with the aid of electrocardiographic monitoring *Am J Med* 37:915, 1964
- Karlsson E Malmström C & Nordgren L A clinical study of a detection system for aberrant QRS complexes *Acta Soc Med Upsal* 75 53 1970
- Kozdi P Waylor, W S Rambousek, R & Stanley E A practical heart rate and ectopic beat detector *J Electrocardiol* 1 213 1968
- Killip T & Kimball J T Treatment of myocardial infarction in a coronary care unit A two year experience with 250 patients *Am J Cardiol* 20 457 1967
- Kühn P Kroiss A & Joskowics G Arrhythmieanalyse - Arrhythmieüberwachung (Vergleichsuntersuchungen von 4 Kleincomputern zur automatischen EKG-Überwachung) *Z Kardiol* 65 166 1976
- Lawrie D M Goddard M Greenwood T W Harvey A C Donald K W Julian D G & Oliver M F A coronary-care unit in the routine management of acute myocardial infarction *Lancet* 2 109 1967
- Liberthson R Nagel E Hirschman J Nussenfeld S Blackburne B & Davis J Pathophysiologic observations in pre-hospital ventricular fibrillation and sudden cardiac death *Circulation* 49 790 1974
- Lindsay J & Bruckner, N V Conventional coronary care unit monitoring Nondetection of transient rhythm disturbances *JAMA* 232 51 1975



- Lorente F Henzel D Bardou A Lesigne E & Levy B : A hardware device for recognition of E and QRS waves Med Progr Technol 4 177 1977
- Lown B Amarasingham R & Neumann J New method for terminating cardiac arrhythmias Use of synchronized capacitor discharge JAMA 182:548 1962
- Lown B Vassaux E Hood W Fakhro A Kaplinsky E & Roberge M : Unresolved problems in coronary care Am J Cardiol 20 494 1967
- Lown B Klein M & Herahberg P Coronary and precoronary care Am J Med 46:705 1969
- MacMillan R L Brown K W G Peckham G B Kahn O Hutchison D B & Paton M : Changing perspectives in coronary care A five year study Am J Cardiol 20:451 1967
- Meltzer L E & Kitchell J B : The incidence of arrhythmias associated with acute myocardial infarction Progr Cardiovasc Dis 9:50 1966
- Mogensen L : Ventricular tachyarrhythmias and lignocaine prophylaxis in acute myocardial infarction A clinical and therapeutic study Acta Med Scand (suppl) 513 1970
- Nacher C Popiliev I Astardjian G Radev C & Gelinov C Quantitative characterisation of heart rhythm disturbances by means of Andros-B a logical rhythm analyser Jap Heart J 12:575 1971
- Neilson J M : An adaptive arrhythmia monitor Computers in Cardiology p 211 IEEE Computer Society 1974
- Nolle F M : The Argus monitoring system: A reappraisal Trends in Computer-Processed Electrocardiograms p 11 North-Holland Publishing Company 1977
- Nygårds M -E Blomqvist P Bulting J Matell G & Wigertz G : Classification of QRS complexes based on a dedicated scheme for feature extraction Computers in Cardiology p 193 IEEE Computer Society 1975
- Nygårds M -E & Bulting J : Recognition of ventricular fibrillation utilizing the power spectrum of the ECG Computers in Cardiology p 393 IEEE Computer Society 1977
- Oliver G C Nolle F M Wolf G A Cox J R & Ambos H D Detection of premature ventricular contractions with a clinical system for monitoring electrocardiographic rhythms Comp Biomed Res 4:523 1971

- of a new computerized arrhythmia monitoring system *Heart Lung* 4 241 1975
- Hulting J , Nygård, M -E & Wigertz, O Problems in the evaluation of arrhythmia monitoring systems *Trends in Computer-Processed Electrocardiograms* p 75, North-Holland Publishing Company 1977
- Jenkins J Wu D & Arzbacher R Computer diagnosis of abnormal cardiac rhythms employing a new P-wave detector for interval measurement *Comp Biomed Res* 11 17 1978
- Jewitt, D Balcon N Raftery E R & Oram S Incidence and management of supraventricular arrhythmias after acute myocardial infarction *Lancet* 2 734 1967
- Julian, D G Valentine P A & Miller G G Disturbances of rate rhythm and conduction in acute myocardial infarction A prospective study of 100 consecutive unselected patients with the aid of electrocardiographic monitoring *Am J Med* 37 915, 1964
- Karlsson S Malmström C & Nordgren L A clinical study of a detection system for aberrant QRS complexes *Acta Soc Med Upsal* 75 53 1970
- Kozdi P Naylor W S Rambousek R & Stanley E A practical heart rate and ectopic beat detector *J Electrocardiol* 1 213 1968
- Killip T & Kimball J T Treatment of myocardial infarction in a coronary care unit A two year experience with 250 patients *Am J Cardiol* 20 457 1967
- Kühn, P Kroiss A & Joskowicz G Arrhythmieanalyse - Arrhythmieüberwachung (Vergleichsuntersuchungen von 4 Kleincomputern zur automatischen EKG-Überwachung) *Z Kardiol* 65 166 1976
- Lawrie, D M Goddard M Greenwood T W Harvey A C Donald K W Julian D G & Oliver M F A coronary-care unit in the routine management of acute myocardial infarction *Lancet* 2 109 1967
- Liberthson, R Nagel E Hirschman J Mussenfeld S Blackburne B & Davis J Pathophysiologic observations in pre-hospital ventricular fibrillation and sudden cardiac death *Circulation* 49 790 1974
- Lindsay J & Bruckner M V Conventional coronary care unit monitoring *Non-detection of transient rhythm disturbances* *JAMA* 232 51 1975

- Lorente P Benzel H Bardou A Lesigne E & Levy B A hardware device for recognition of P and QRS waves Med Progr Technol 4:177 1977
- Lowy B Asarasingham R & Neumann J New method for terminating cardiac arrhythmias Use of synchronized capacitor discharge JAMA 182 548 1962
- Lowy B Vassaux C Hood W Fakhro A Kaplinsky E & Loberge G Unresolved problems in coronary care Am J Cardiol 20:494 1967
- Lowy B Klein M & Herahberg P : Coronary and precoronary care Am J Med 46:705 1969
- MacMillan R L Brown E W G Peckham G B Kahn O Hutchinson D B & Paton M : Changing perspectives in coronary care A five year study Am J Cardiol 20:451 1967
- Meltzer L E & Mitchell J B : The incidence of arrhythmias associated with acute myocardial infarction Progr Cardiovasc Dis 9:50 1966
- Mogensen L : Ventricular tachyarrhythmias and lignocaine prophylaxis in acute myocardial infarction A clinical and therapeutic study Acta Med Scand (suppl) 513 1970
- Nacher C Popiliev I Astardjian G Radev C & Gelinov C Quantitative characterisation of heart rhythm disturbances by means of Andros-R a logical rhythm analyser Jap Heart J 12:575 1971
- Neilson J M : An adaptive arrhythmia monitor Computers in Cardiology p 211 IEEE Computer Society 1974
- Nolle F M : The Argus monitoring system A reappraisal Trends in Computer Processed Electrocardiograms p 11 North-Holland Publishing Company 1977
- Nygårds M -E Blomqvist P Hulting J Matell G & Wigertz O : Classification of QRS complexes based on a dedicated scheme for feature extraction Computers in Cardiology p 193 IEEE Computer Society 1975
- Nygårds M E & Hulting J : Recognition of ventricular fibrillation utilizing the power spectrum of the ECG Computers in Cardiology p 393 IEEE Computer Society 1977
- Oliver G C Nolle F M Wolf G A Cox J R & Ambos H D Detection of premature ventricular contractions with a clinical system for monitoring electrocardiographic rhythms Comp Biomed Res 4:523 1971

- Quinn M L Haring, O M & Lewis F J Evaluation of computer diagnosis of ectopic beats encountered in routine patient monitoring *Comput Biol Med* 5 235 1975
- Raftery E B Rehman M F Banks D C & Oram S Incidence and management of ventricular arrhythmias after acute myocardial infarction *Br Heart J* 31 273 1969
- Restieaux N , Bray, C Bullard H Murray M , Robinson J Bridgen W & McDonald L : 150 patients with cardiac infarction treated in a coronary unit *Lancet* 1 1285 1967
- Ripley, K L & Arthur R M Evaluation and comparison of automatic arrhythmia detectors *Computers in Cardiology* p 27 IEEE Computer Society 1975
- Ripley K L & Oliver G C Development of an ECG database for arrhythmia detector evaluation *Computers in Cardiology* p 203 IEEE Computer Society 1977
- Romhilt, D W Bloomfield S S Chou T -C & Fowler, N O Unreliability of conventional electrocardiographic monitoring for arrhythmia detection in coronary care units *Am J Cardiol* 31:457 1973
- Rompelman O Coenen A & Saat R A special-purpose computer for on-line statistical analysis of the heart rate *Med Progr Technol* 5 149 1977
- Ryden L Hjalmarsson A & Waldenström A Effects of the quaternary ammonium compound QX-572 on ventricular tachyarrhythmias complicating acute myocardial infarction *Br Heart J* 37 426 1975
- Sanders W , Alderman E & Harrison D C Alarm processing in a computerized patient monitoring system *Computers in Cardiology* p 21 IEEE Computer Society 1976
- Sanders W Alderman E Harrison D C & Dillman R Computerized processing of artificially paced ECG rhythm *Computers in Cardiology* p 435 IEEE Computer Society 1976
- Shah P Arnold J Haberer N Bliss D McClelland K & Clarke B Automatic real time arrhythmia monitoring in the intensive coronary care unit *Am J Cardiol* 39:701 1977
- Spann J F Moellering R C Haber E & Wheeler E O Arrhythmias in acute myocardial infarction A study utilizing electrocardiographic monitor for automatic detection and recording of arrhythmias *New Engl J Med* 271 427 1964
- Stanton P Tinker J Vickery J C & Vahl, S P The Seat-

- tergram A new method for continuous electrocardiographic monitoring Cardiovasc Res 6:598 1972
- Stock E Goble A & Bloomer G Assessment of arrhythmias in myocardial infarction Brit Med J 2 719 1967
- Vaisrub S: Electrocardiographic monitoring - bad news and good news (Editorial) JAMA 232:57 1975
- Vetter M J & Julian D G Comparison of arrhythmia computer and conventional monitoring in coronary care unit Lancet 1:1151 1975
- Vigertz O Blomqvist P Rulding J Matell G Rygård M E & Törnkvist G : A computer-based system for continuous ECG monitoring Medinfo 1974 p 761 North-Holland Publishing Company
- Wiklund B : Medically unattended fatal cases of ischemic heart disease in a defined population Acta Med Scand (Suppl) 524 1971
- Yanowitz F Kinias P Rawling D & Foxzard H A Accuracy of a continuous real time ECG dysrhythmia monitoring system Circulation 50 65 1974
- Zeeenberg C Deutsch L S Engleess W A H & Corbeij H M A Experiences with implementing ARGUS in a cardiac surveillance unit Trends in Computer-Processed Electrocardiograms p 31 North-Holland Publishing Company 1977
- Zoll P M Libenthal A J Gibson W Paul M H & Norman L R : Termination of ventricular fibrillation in man by externally applied electric countershock New Engl J Med 254 272 1956



